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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 29 1961

THE CONNECTIVE TISSUE*

BY

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Klemperer and his colleagues (1942) were the first to draw attention to the possibility that certain conditions with common morphological aspects could be due to widespread disorders of the connective tissue, and thus was born the appellation "collagen diseases." The clinical similarities in conditions with these like pathological findings were quickly recognized, and rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, progressive systemic sclerosis (scleroderma), and dermatomyositis have, by more or less general consent, been grouped as diffuse disorders of the connective tissue for some years. Some others have been added to them with the passage of time, examples being thrombotic thrombocytopenic purpura and relapsing febrile nodular non-suppurative panniculitis (Weber–Christian disease).

It was, however, realized from the first that common pathological changes, and even similar clinical features, were no evidence that these states had a common aetiology, and an additional objection was raised to this grouping of diseases on the score that more than collagen, or even connective tissue as a whole, was involved. The substitution of the term "connective tissue diseases" for "collagen diseases" thus did not satisfy the critics. In spite of the various distortions of his original conception, Klemperer (1956) once more supported his contention that this grouping was useful in that it introduced a concept of a diffuse intercellular pathology, whereas previously attention had been devoted exclusively to the cellular aspects of these conditions. Neuberger (1960) has given his support to Klemperer's conception, and so has Robb-Smith (1960) in a carefully reasoned argument.

Most clinicians also would wish to preserve this grouping, at any rate for the present, as it provides a starting-point for the consideration of certain complex clinical problems.

Before turning to the discussion of the little which is known of the aetiology and pathogenesis of the connective-tissue disorders, it is necessary to review some of the knowledge which is reasonably established concerning the fundamental aspects of connective tissue.

The connective-tissue system forms a continuous matrix throughout the body, and includes the bones, cartilages, the loose connective tissue of the skin, the tendons, ligaments, fascia, joint capsules, and the capsules of organs. The content of collagen in structures varies with the degree of strength which is required from them. Collagen in tendons, for instance, amounts to 25 to 35% of their total wet weight, whereas in the vitreous humour it constitutes only 0.05% (Slack, 1959).

The connective tissue consists of three elements—cellular, fibrillary, and the ground substance. These are all closely associated with epithelial and other tissues, such as blood vessels, lymph vessels, and nerve fibres, and this is evidenced by the clinical studies of the so-called connective-tissue diseases, in many of which vascular disorders dominate the clinical picture. Some of the morphological and biochemical characteristics of the cellular and fibrillary elements, and of the ground substance, have already been reviewed (Richardson, 1959).

Cellular Elements

The cells of the connective tissue are of two types—the fibroblasts and the mast cells. Fibroblasts are the more numerous cells, and their main function is the formation and liberation of collagen into the extracellular spaces. They contain in their cytoplasm granules composed of mucopolysaccharides and protein, and it is possible that these granules are responsible for the development of collagen fibrils, but this is still unproved.

The other cells, the mast cells, are mesenchymal in origin. They contain metachromatic granules in their cytoplasm which stain with basic dyes such as toluidine blue. These granules are composed of mucopolysaccharides which enter the ground substance from the mast cells. The mast cells are associated with sulphate metabolism and may be responsible for the storage of heparin and the secretion of hyaluronic acid, and are probably concerned with histamine release. The function of the mast cells therefore appears to be related to the ground substance rather than to fibril formation.

Fibrillary Elements

These are believed to be produced entirely by the fibroblast, which is thought to be solely responsible for the formation of different fibres, which may be collagenous, reticular, or elastic.

Collagen

The electron microscope has greatly altered and enlarged our conception of the appearances of connective tissue. Its use has demonstrated that the collagen fibril is approximately 1,010 Ångstrom units in width, and is characterized by regularly occurring cross-striations spaced at intervals of 640 Ångstrom units (an Ångstrom unit is 0.1 mμ). This particular spacing is constant for collagen for human tissue from whatever site it is taken. There are also inter-period bands between the 640-Ångstrom-unit period; but here the

*Based on a paper read before the Annual Clinical Meeting of the British Medical Association at Middlesbrough on October 7, 1960.

number is not fixed, and the different numbers of bands probably indicate differences of chemical structure.

The width of collagen fibrils varies with different structures but tends to increase with age. Age also affects the destructive action of the enzyme collagenase on collagen, as it is greater in young tissue, and the increased susceptibility of collagen to this enzyme below the age of 25 years might afford an explanation for the vulnerability of collagenous structures in young heart valves in such conditions as rheumatic fever. The effect of age on connective tissue depends to some extent on the gradual reduction of the very high water content which is present in the embryo, and this is thought to lead to the side-chains of the polypeptides becoming drawn together and losing some of their physical and chemical activity. On the basis of this view ageing of the connective tissue is a drying-out process.

Chemically, collagen is protein and contains over 25% of the amino-acid glycine, and has a high hydroxyproline and proline content.

The polypeptic chain of collagen is stabilized by cross-linkages with other adjacent chains. The effective linkage is the hydrogen bond between the NH group of one chain and the oxygen of a carbonyl group of another. When these hydrogen bonds are disrupted by heat the collagen fibre shrinks and takes up its natural shape, that of a random coil. The estimation of the shrinkage temperature (T_s) at the level where shrinkage begins (T_{s1}) and where it ends (T_{s2}) is a means of determining the effect of various substances on collagen. It has been shown that a reduction in shrinkage temperature can be achieved by hydrogen-bond breakers, and Glynn (1959) has found that sodium salicylate and related compounds are the most active.

When a collagen fibre has shrunk—that is, has had its hydrogen bonds broken—it is, *in vitro*, readily digested by proteolytic enzymes such as trypsin. It is possible that, *in vivo*, dissolution of collagen is preceded by the action of some hydrogen-bond breaker (Glynn, 1959).

The fibrous protein of collagen is highly resistant to proteolytic enzymes and to absorption *in vivo*. The structure and stability of collagen have been reviewed by Glynn (1959), who studied the resistance to absorption of collagen by means of implants. He found that collagen—that is, facial strips, taken from a freshly killed rabbit and implanted subcutaneously—persisted virtually unchanged for 13 weeks, with an almost identical appearance after over a year, whereas subcutaneous implants of liver and heart muscle disappeared in four weeks, and of kidney in six weeks. When the implants were made in the erector spinae muscle, only fascia remained after four weeks.

Neuberger and Slack (1953) had previously demonstrated the stability of collagen in another way by showing how extremely slow was the turnover of limb collagen when glycine labelled with the radioactive isotope C-14 was fed to adult rats.

Reticulin and Elastic Fibres

The second fibre in the connective tissue is the reticular fibre, sometimes called reticulin as it forms a fine network or reticulum. The reticular fibre contains carbohydrate, and this can be demonstrated by various oxidative methods, and has a cross-striation under the electron microscope similar to that of collagen. There is evidence in support of the suggestion that the fibrillary element of reticulin is a variety of collagen, having a similar protein constitution, but there is an abundant amorphous matrix in reticulin, rich in carbohydrate, in which the arrangement of the reticular fibrils is random and unlike the orderly parallel bundles of collagen.

The third element, elastic tissue, has a different appearance from collagen under the electron microscope, and also a different chemical composition, containing more of the amino-acid valine, and less hydroxyproline and proline.

The Ground Substance

Alteration in the chemical composition and physical properties of the ground substance is probably the basis of many of the connective-tissue disorders.

The mast cell is thought to be responsible for the production of ground substance, but it may not be solely concerned, as there is some evidence that fibroblasts may play a part. The ground substance, lying between the meshes formed by the fibrils of the various fibrillar structures which constitute the protein framework of the connective tissue, contains protein derived from the extracellular fluid, together with a high content of mucopolysaccharides, chiefly hyaluronic acid, chondroitin sulphate, A, B, and C chondroitin, and keratosulphate. It also contains mucopolysaccharides and protein complexes known as glycoproteins. These glycoproteins tend to be the least soluble at the basement membrane, where they are in close relationship with collagen and reticulin fibres.

The ground substance is normally the consistency of a gel, and stains metachromatically, both hyaluronate and sulphate mucopolysaccharides staining in this way, but in certain disorders it loses this staining characteristic. Scurvy is an instance of this, the ground substance ceasing to stain metachromatically. Further evidence of alteration in the ground substance in this disorder is an increase of glycoproteins in the blood.

Hyaluronic acid is responsible for certain physicochemical properties of ground substance—namely, its water-binding capacity, its gelatinous character, and its viscosity. It appears to act as a lubricant and, as Karl Meyer (1954) says, a shock-absorber.

Changes in the permeability of the ground substance can be effected by means of the enzyme hyaluronidase, which increases permeability by removal of hyaluronic acid from the meshes of the protein fabric. This process can be reversed by diffusion with large macromolecules, which suggests that flow takes place through spaces of such a size that they can be blocked more readily by large macromolecules than by smaller ones.

The endocrine glands have their influences on the chemical state and function of the connective tissue, and various well-recognized clinical features depend upon this.

In severe cases of hypopituitarism and in pretibial myxoedema the collagen bundles and elastic fibres may be swollen and degenerate, with an increase in the hyaluronic acid and chondroitin acid content of the ground substance and in the number of mast cells in it. Examination of the ground substance shows a reduction in mucopolysaccharides and mast cells, as well as degeneration of the collagen and elastic fibres, which stain poorly. Hormonal deficiency or overactivity, therefore, can express itself in marked changes in the connective tissue, and especially in the ground substance.

The wide purple striae found on the abdomen and around the hips and shoulder girdles in adrenal hypercorticoidism are due to a reduction in the tensile

elasticity and strength of the skin. Histologically the skin is atrophic, and the ground substance contains little mucopolysaccharide. Mast cells are usually scanty and the connective tissue as a whole acellular. Both collagen fibrils and elastic fibres show degenerative signs and stain faintly. The connective tissue, therefore, and the ground substance in particular, is severely affected by deficient or overactive hormonal influences.

Neuberger (1960) has expressed the view that, interesting as are the studies in changes in collagen synthesis or its breakdown, the biochemistry of the components of the ground substance, such as the mucopolysaccharides, is likely to be of greater importance in elucidating the essential factors in the connective-tissue disorders. Further, he suggests that the same might well be true of the study of immunological reactions and of systemic antibodies.

Antigenicity of Connective Tissue

Immuno-histochemical techniques have been used to investigate the antigenicity of connective tissue (Scott, 1959). This technique depends on labelling a specially prepared antibody globulin with a substance which will fluoresce under the fluorescent microscope. If the fluorescing antibody globulin is then exposed to tissue containing its specific antigen, it will be fixed by the antigen and the site of the antigens identified by fluorescent microscopy. Using two different labels on different preparations of antibody globulin, Scott was able to recognize three connective-tissue antigens or groups of antigens. These he called basement membrane antigen, reticulin antigen, and fibrous-tissue antigen.

The basement membrane antigen reacted only with antiglomerulous conjugates. The other two reacted not only to antiglomerulous conjugates, but also to anti-synovium, the difference between them being that fibrous-tissue antigen reacted preferentially with anti-synovium whereas reticulin did not.

Scott makes it clear that there is not as yet enough information to enable any correlation between results obtained by immuno-histological methods with ones from chemical and physico-chemical analyses. This method of investigating the properties of connective tissue is, however, likely to yield much valuable information in the future.

Evidence of hypersensitivity has been put forward as aetiologically significant in each of the conditions commonly included as connective-tissue disorders. There is in fibrinoid degeneration a pathological change common to all these disorders and to allergic reactions. This change is not, however, confined to these conditions, and is found in such diverse states as malignant hypertension and thromboangiitis obliterans, where it affects the vessel walls, in inflammations of serous, mucous, synovial, and endothelial surfaces, in the base of peptic ulcers, and also in hygromas. It has been described in addition in the placenta, although the fibrinoid material in this situation is regarded as being of a different character to that found elsewhere. It can be produced by trauma to tissue such as squeezing, or by prolonged passive hyperaemia. It is seen in various acute bacterial infections and has followed the use of large doses of deoxycortone acetate.

It is clear, therefore, that fibrinoid change is not specific for any particular group of disorders, although it occurs regularly in allergic conditions.

There is evidence that fibrinoid material contains inspissated fibrin as one of its constituents. Other suggestions are that fibrinoid may be due to changes in ground substance or to necrosis of collagen, or to a combination of these processes together with the products of degenerated smooth muscle.

Study of rheumatoid nodules by *x*-ray defraction technique suggests that when the fibrinoid change is far advanced there is complete destruction of collagen, whereas in the intermediate stages the *x*-ray pattern shows the presence of amorphous material and disintegrating collagen fibres.

Chemically, fibrinoid material lacks both proline and hydroxyproline, and in this it does not resemble collagen. It also has no close resemblance to collagen under the electron microscope. Under the light microscope it appears as a homogeneous eosinophilic and relatively acellular refractile substance. It has some of the tinctorial properties of fibrin, and it was these appearances and staining properties that led to its introduction as a descriptive term.

There is some evidence of hypersensitivity in the therapeutic response of most of the so-called connective-tissue diseases, as well as frankly allergic states, to corticosteroids or corticotrophin. Drugs such as testosterone, sulphonamides, the antibiotics, and the thiouracils have been indicated as causative agents in the development of polyarteritis nodosa, and the rise in the incidence of systemic lupus erythematosus has been attributed to the increased use of the sulphonamides and of antibiotics, notably penicillin. Again, a condition closely similar to that of systemic lupus erythematosus has been shown to follow the use of the hypotensive drug hydrallazine.

These associations could have a basis in hypersensitivity, as it has been shown that a hapten, a non-antigenic substance foreign to the body—for example, a drug—can combine with a body protein, and by so doing render it antigenic.

The presence of the rheumatoid arthritis factor and of the two lupus erythematosus cell factors in systemic lupus erythematosus (Bencze *et al.*, 1959) suggests that there are circulating antibodies in these two conditions.

Whether or not the rheumatoid arthritis factor and the lupus erythematosus factor are more than interesting by-products of these conditions remains to be decided, and it must be admitted that the level in the blood of the rheumatoid arthritis factor does not parallel the clinical course of these diseases, and its addition does not increase the severity of the patient's condition. Furthermore, the transmission of the factor to volunteers has not produced the disease, and people can carry the rheumatoid arthritis factor without having any clinical manifestations of the disease—so-called false-positive individuals. These are sometimes the siblings of patients with rheumatoid-arthritis-factor-positive rheumatoid arthritis.

Auto-immunity

The possibility that an auto-immune reaction may be the underlying process has been recently suggested.

An auto-immune reaction was first demonstrated in Hashimoto's thyroiditis. Antibodies were shown to have been produced against, not foreign protein, but one of the body's own components, in this instance thyroglobulin. There thus must be some mechanism normally present which allows the body's immunological processes to distinguish between its own products and foreign ones,

as otherwise there would be a constant production of auto-antibodies. Until recently the idea that this could ever happen was contrary to all accepted immunological theory, and speculation now centres about the nature of the normally efficient mechanism for distinguishing between "self" and "not self."

It has been shown that the power of antibody-forming tissue to react is largely dependent on the presence of antigens at the time the tissues reach maturity, and that tolerance can be induced by presenting the tissues with antigen some time before the production of antibodies begins. This is somewhere round about the time of birth. It is possible that if the antigen cannot gain access to antibody-producing tissues at this time no tolerance is acquired, and later in life the antigen from the person's own tissues may lead to antibody production.

Macfarlane Burnet (1959), in his clonal selection theory of immunity, has suggested that body cells possess specific immunological properties or competence which are genetically determined. The antigen, according to this theory, does not, as in the classical theory of immunity, imprint its pattern by imparting information which results in the production of an antibody complementary to itself, a template, but it simply stimulates certain mesenchymal cell clones which are genetically determined to respond by antibody to it. A clone can be defined as a group of individuals of like genetic constitution obtained by asexual reproduction from a single original individual. When the clones multiply either their destruction may result, as normally happens, or proliferation may take place and a disease process follow. The clones of cells are called "forbidden clones" if the production of their union with antigen does not lead, as it normally does, to their destruction and elimination from the body, but rather to their proliferation and the further production of antigen, with the establishment of a vicious circle.

The antigen therefore, according to this theory, stimulates cells to produce the specific antibody which they have been genetically determined to produce, and does not itself determine the specificity of the antibody.

An alternative hypothesis is that antibody-producing cells may undergo somatic mutation themselves, with the result that they produce auto-antibodies and thus auto-immune disease.

Auto-immunity is an attractive theory by which to explain the association of neoplasms with dermatomyositis, and the presence of widespread vascular lesions with thromboses in patients with malignant growths. It could be postulated that the neoplasm produces breakdown products to which cells either lose their immunological tolerance or have genetically determined specific immunological properties.

That auto-immunity can occur is beyond doubt, but the nature of the breakdown of the normal mechanism existing to prevent the continual production of auto-antibodies is far from certain. It is also uncertain whether the auto-immunity is primary and a causative factor, or secondary and the result rather than the cause.

The position concerning the presence and significance of various and increasingly numerous auto-immune reactions in systemic lupus erythematosus has been reviewed most profitably in the *British Medical Journal* (1960). There can be some overlap between thyroid antibodies and antinuclear antibodies in Hashimoto's disease, and between the antinuclear factors and the rheumatoid arthritis factor in both systemic lupus erythematosus and rheumatoid arthritis. It seems that the evidence at present suggests that in systemic lupus erythematosus, at any rate, auto-immune antibodies are the result rather than the cause of the disease.

The evidence that the connective-tissue disorders are in part due to auto-immunity, or even to hypersensitivity, is thus very far from complete, and it is sobering to reflect that if the role of hypersensitivity is disproved there is little at present to put in its place.

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ATHEROSCLEROSIS: RESULTS OF A PILOT SURVEY IN A NORTH LONDON AREA

BY

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The object of this survey, which was exploratory and limited in extent, was to examine the pattern of aortic atherosclerosis as it presented in a North London area, so as to study its natural history and to see if it differed in any way from that found in other parts of the world.

Currently, several surveys of atherosclerosis are being carried out on a geographical basis so as to ascertain the importance of the various factors of race, climate, terrain, social behaviour, and diet as aetiological agents in this disease (W.H.O., 1958), if, indeed, atherosclerosis is a disease as distinct from the physiological process of ageing.

As it is impossible to examine the progress of the disease in its various stages in the same human subject the only recourse is to examine trends in several hundreds of patients at necropsy. As is recounted below, there have been difficulties in assessing the extent and severity of the various lesions, both objectively and precisely, so as to be reproducible in the form of mathematical data.

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Notwithstanding these difficulties, the trends appearing from our survey suggest that the deposition of fat in the fourth and fifth decades is a factor of great importance, for at this period of life the lipid present (atheroma) has a tendency to fibrosis (atherosclerosis), and ultimately to the pathogenesis of more complicated lesions in later life.

Materials and Methods

A total of 382 aortas (206 male, 176 female) were examined. The majority were obtained from the public mortuaries, although a few came from several hospitals in the North London area. The cause of death was not taken into account for their selection. The aorta was opened and the whole of the intimal surface examined; the artery was then stained by Sudan IV for 15 minutes by the method recommended by Gore and Tejada (1957).

Histological examination was made of representative samples of specimens, prepared in the usual manner and stained by the following methods: H. and E., P.A.S., Mallory's phosphotungstic acid haematoxylin, toluidine blue, Hale's acid-mucopolysaccharide, Van Gieson and Verhoeff, and Von Kossa. Frozen sections were stained with Sudan IV for fat, and examined under the polarizing microscope for cholesterol crystals. The extent and severity of the lesions was assessed by a modification of the method suggested by Gore and Tejada. This assessment, briefly, was as follows:

Extent of Atherosclerosis		*Type of Lesion*	
Group	Proportion of Intima Diseased		
O	.. Less than 5%	Grade 1: Fatty deposits (streaking)	
A	.. 6 to 15%	,, 2: Fibrous plaques with or without fat	
B	.. 16 to 33%	,, 3: Plaques with ulceration necrosis, haemorrhage, or thrombosis	Complicated lesions
C	.. 34 to 50%	,, 4: Calcified plaques	Complicated lesions
D	.. More than 50%		

The "atherosclerotic profile" suggested by Gore and Tejada was also adopted. This consisted of a group letter followed by a number, each of whose four digits corresponded respectively and sequentially with one of the grades of lesions. Thus, D 1,4,3,2 refers to an aorta which had more than 50% of its surface area involved, of which one-tenth of the lesion was made up of fatty deposits (grade 1), four-tenths of fibrous plaques (grade 2), three-tenths with ulcerative or haemorrhagic lesions (grade 3), and two-tenths with calcification (grade 4).

Results and Comments

Type of Lesion

The relative incidence of the various types of lesion is given in Table I and Fig. 1. In these the numbers listed under fatty lesion are the numbers of cases in which fatty lesions were found alone; those under fatty-fibrous plaques were those in which discrete fatty lesions (grade 1) and discrete fatty-fibrous lesions (grade 2) *together* were found; and those under complicated lesions were those in which *all* types of lesion were found together—that is, grades 1, 2, 3, and 4.

Fatty deposits were found as early as the first year of life, and appear to be almost the only type of lesion in the first and second decades. One case with fibrous plaques containing fat was found in the 11–20-year age-group, but this patient was 20 years old. In the first decade only about half the cases were affected, but by the second decade nearly all cases were involved.

Fatty streaking was prominent during the third decade, at which time, however, the incidence of fibrous plaques appeared to be increasing. An analysis of the ages of the patients in this group revealed that most of the cases with fibrous plaques were in the last five years of the decade.

By the fourth decade the incidence of cases with fatty deposits alone and fatty-fibrous plaques was about equal. In this decade two patients had complicated lesions, but they were aged 38 and 40.

During the fifth decade the relative incidence of fatty deposits as the only lesion present had fallen considerably, and the main lesions were both fatty-fibrous plaques and complicated lesions. However, an examination of the age-groups of the patients with the complicated lesions showed that the majority were in the last five years of the decade.

In the sixth decade, only two patients, aged 51 and 54, had discrete fatty lesions alone, and the incidence of cases with both fatty and fatty-fibrous plaques had begun to fall, with a corresponding rise in the incidence of complicated lesions, so that in the sixth decade onwards the majority of all cases showed lesions of the complicated type.

No particular significance in incidence was found in relation to sex or to the onset of puberty; a further investigation with greater numbers should be done before accepting this statement as valid.

TABLE I.—*Incidence of the Various Types of Aortic Atherosclerosis*

Age-Group	Total No. of Cases	Normal	Fatty Lesions	Fatty-Fibrous Plaques	Complicated Lesions
S.B.	15	100% (15)	—	—	—
<1	28	75% (21)	25% (17)	—	—
1–10	11	45% (5)	55% (6)	—	—
11–20	15	—	93% (14)	7% (1)	—
21–30	31	—	77% (24)	23% (7)	—
31–40	31	—	42% (12)	52% (17)	6% (2)
41–50	54	—	8% (4)	46% (25)	46% (25)
51–60	64	—	3% (2)	34% (22)	63% (40)
61–70	46	—	—	7% (3)	93% (43)
71–80	62	—	—	—	100%
81–100	25	—	—	—	100%

Figures in parentheses indicate total number of cases in each category.

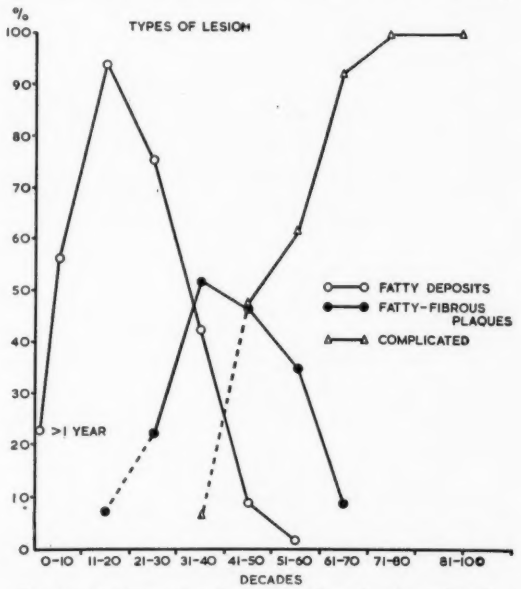

FIG. 1.—Incidence of various types of aortic atherosclerosis.

From the foregoing it would seem that fatty deposition increases *de novo* as age progresses, but some authors (Aschoff, 1925) claim that the fatty deposits of infancy are reversible, especially the deposition of fat at the aortic ring. The following summarizes our findings in this area. Incidence of fatty deposition at aortic ring: under 1 year, 20%; 1–10 years, 40%; 11–20 years, 75%; and 21–30 years, 100%.

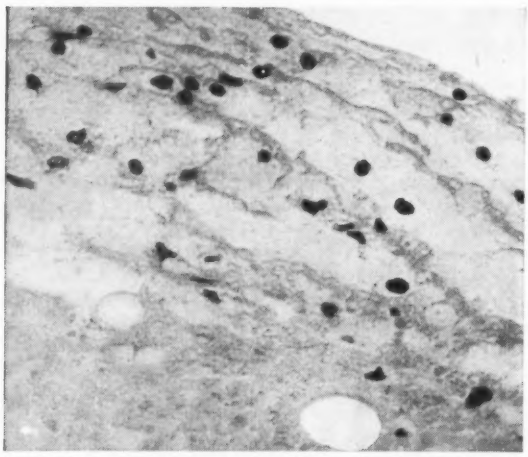

FIG. 2.—Fatty streaking; showing foam cells subintimally with no cellular reaction. (H. and E. ×450.)

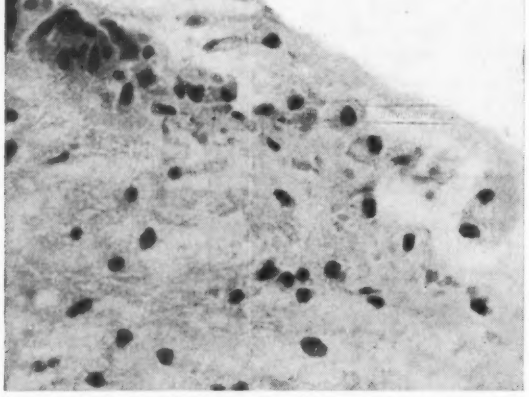

FIG. 3.—Fatty deposit with early cellular reaction. (H. and E. ×450.)

FIG. 4.—Fibrous plaque with central fat. It is believed that the fibrosis is secondary to the fat. (Frozen section; Sudan IV. ×66.)

It can be seen that the incidence of fatty deposition at the aortic ring progresses with age, and it is unlikely that the original deposits of infancy disappear, to be redeposited at a later age—that is, it is probable that they are irreversible.

Extent of the Lesions

The extent of the lesions was estimated for each case by the method of Gore and Tejada (1957) as an "atherosclerotic profile." Table II gives the percentage of cases in each decade, falling in the different categories of surface area involved—that is, groups O, A, B, C, and D.

TABLE II.—*Percentage of Cases Showing Areas of Intimal Surface Involvement, as Indicated by "Atherosclerotic Profiles"*

Age-Group	Total No. of Cases	Group				
		O	A	B	C	D
<1	28	100				
1–10	11	80	20			
11–20	15	35	55	15		
21–30	31	25	35	25	15	
31–40	31	15	20	35	20	10
41–50	54	5	10	40	35	10
51–60	64	0	10	30	20	40
61–70	46	0	5	20	15	60
71–80	62	0	5	5	20	70
81–100	25	0	5	10	30	55

It will be seen that there is an increased extent of involvement with increase of age. Thus by the fourth decade 10% of cases have more than half of their intimal surface involved, and by the sixth and seventh decades almost half the cases have such an extensive involvement.

When these figures are correlated with Table I it can be inferred that the increase in incidence of fatty deposition in the first and second decades is associated with either an increase in the number of deposits or an increase in the size of the deposits already present, or both.

Gross inspection, however, indicated that the increase in involvement was mainly due to an increase in the number of new lesions. Also, in the third and fourth decade there was observed an increase in the incidence of fibrous plaques (grade 2) (Table I, Fig. 1), as well as an increase in extent of area involvement (Table II). Was this due to fibrous plaques appearing *de novo* or to a fibrous reaction to the fatty deposits?

Histologically, examination of representative plaques in the first two or three decades showed the presence of fat with little or no cellular reaction (Fig. 2). In the fourth and fifth decades there seemed to be generally a fibrous-tissue reaction to the presence of fat (Figs. 3 and 4). By the fifth decade onwards the fibrous reaction had become more pronounced and was associated with degenerative changes and thrombosis, haemorrhage, necrosis, and calcification, with a reactive chronic inflammation.

Discussion

This study, within its limitations (and there are disappointingly many), has shown that the deposition of fat within the intima is the earliest lesion (atheroma), and that this lesion progresses, both in severity and in extent, with age.

It would seem from histological observation and analysis of our data (arrived at by subjective appraisal)

that there was a progression of events from fatty deposition to fibrosis to complicated lesions, in that order, and as distinct but overlapping phases. These observations are supported in the main by those of Strong *et al.* (1958) in their studies involving the aortas from patients in New Orleans, Guatemala, and Costa Rica.

In the younger age-groups there was no macroscopic or microscopical evidence of fatty deposition being secondary to organization of thrombi, haemorrhage, or fibrosis, but all evidence in our hands suggested that the deposition of fat occurred *de novo*. Thrombotic and haemorrhagic causes of atherosclerosis appear to be significant only in the older age-groups, from the fifth decade onwards.

We have concluded tentatively that fatty deposition is possibly not reversible, but further observations are necessary before we can be certain.

The presence of fatty deposits in the first, second, and even the third decades, generally without any reaction, appears to us to be physiological and harmless. Fibrosis (to any extent) appears only in the middle of the third to the middle of the fourth decade, and is well established by the fifth. Later, there is the development of the complicated lesions which become evident during the sixth decade, and are possible complications of the lesions arising in the previous phase.

An explanation of the above conclusions which is most favoured by us is that there are different reactions of the body at different ages. Aschoff (1925) has postulated three stages of ageing in the aorta. The first was an "ascending period" from birth to 33 years, during which there was, generally, a physiological increase in all tissue elements. The second was a "summit period" from 33 to 45 years, when the aorta retains its form. The third was a "descending period" after 45 years, in which the aorta becomes overstretched and dilated—"simple sclerosis" or "senile ectasia." The intimal reaction to this is an increase of connective and elastic tissue elements with degeneration and hyalinization. He found that deposition of intimal fat occurred at all ages.

The first part of the ascending period, which he called the "atheroma of infancy," he believed to be reversible. At a later period, from 16 to 33, and even to 40 years, which he named the "atheroma of puberty" or "youth," he found fatty deposition with very little reaction, which he considered might or might not prove to be reversible. However, in the descending period of life—that is, over 45 years—he found that the deposition of fat engrafted on the changes of physiological ageing resulted in "atherosclerosis" or "destructive sclerosis," which is irreversible.

It appears to us that Aschoff's conclusions help to explain our findings that the symptomless and harmless mild fatty deposits of the first part, or ascending period, of life tend to become pathological in the summit, or second period, due to fibrosis, and later become complicated in the third phase, the descending period.

If this is so, then it would seem that efforts should be directed to the study of the deposition of fat in the intima, particularly during the fourth and fifth decades. Before this age it does not seem to matter much, but after that it would appear that the complicated lesions of the descending period of life are all-important.

Added emphasis is given to this aspect of the disease when the results of Strong *et al.* (1958) are taken into consideration. In their studies they compared the natural history of the disease between residents of the U.S.A. (New Orleans) and Central America (Costa Rica and Guatemala). They found that the deposition of intimal fat followed a similar pattern in both geographical areas. Their findings are, in general, similar to ours, except that they place importance on a greatly increased deposition of fat in the second decade which they believe may be due to the hormonal changes of puberty.

However, the cases from the U.S.A. had fibrous plaque formation much more advanced and extensive in the third and fourth decades than those in the cases from Central America. It would seem that fibrous-plaque formation in the cases we examined from North London are similar to those from New Orleans and different from those from Central America. Strong *et al.* suggest that fatty deposition may not be a function of the fat content of the diet or a function of race; they believe, however, that diet may be important in the genesis of fibrous plaques. They stress the importance of further studies in the factors influencing the conversion of fatty streaks to fibrous plaques, an opinion which we endorse.

Summary

A total of 382 aortas from a North London area were examined, both macroscopically and microscopically. Fatty deposits appeared to develop irreversibly as early as the first year of life, and increased in incidence as a lesion to involve *almost every* patient in the second decade.

In the third decade, particularly in the second half, fibrous plaques made their appearance, and by the fourth decade the incidence of cases with either fatty or fibrous lesions was about equal.

In the fifth decade, particularly in the second half, complicated lesions made their appearance, and did so increasingly, so that almost all patients had this lesion by the seventh decade.

It is suggested that the pathogenesis of the disease is the deposition of fat within an intima of different reacting capabilities, which latter is associated with age. In the early age-groups there is no reaction, but in the third, fourth, and fifth decades there is a fibrous-tissue reaction to the fat, leading to sclerosis. The reaction in the sixth decade and later is one producing complications.

It would seem that the disease, as found in North London, is similar to that found in other parts of the world from which studies have been reported, and, in particular, very much like that in New Orleans.

It is suggested that further studies should be directed on the factors influencing the conversion of fatty streaks to fibrous plaques.

Acknowledgment for the help given in this survey is made to Sir W. Bentley Purchase and Dr. R. I. Milne, H.M. Coroners, St. Pancras; to Drs. C. C. S. Pike and W. B. Obank, of Peace Memorial Hospital, Watford, and Dr. R. F. Welch, of Barnet General Hospital; to Mr. Phillips, for photographic work; to Miss Haestier and Miss Katherine Hill, for the secretarial work; and to the Board of Governors of the Royal Free Hospital for the award of funds for research.

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EFFECT OF D-THYROXINE ON THYROTOXICOSIS AND ON THE ASSOCIATED EXOPHTHALMOS

BY

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D-Thyroxine, the optical isomer of the naturally occurring L-thyroxine, has aroused considerable interest because of the reported dissociation of its calorigenic effect from its other effects (Boyd and Oliver, 1960). A marked decrease of the radioiodine uptake by the thyroid has been observed after administration of D-thyroxine (Starr and Liebhold-Schueck, 1953). In some thyrotoxic patients treated with D-thyroxine Greene and Farran (1958) observed a fall in thyroid radioiodine uptake accompanied by a remission of symptoms, which they attributed to a decreased production of thyroid-stimulating hormone. If D-thyroxine can be shown to be effective in the treatment of thyrotoxicosis it would have advantages over antithyroid drugs at present in use, since it would be a more rational form of treatment and, moreover, should not give rise to sensitivity reactions.

In order to assess the possible value of D-thyroxine in the treatment of thyrotoxicosis, we have followed the clinical progress of patients given this drug, using the therapeutic index devised by Crooks *et al.* (1960). We have also treated a small group of thyrotoxic patients with iodine in amounts equivalent to that contained in the doses of D-thyroxine. Estimations of the absolute iodine uptake (A.I.U.) in μg. of stable iodine per hour were carried out in order to determine whether any reduction in radioiodine uptake (% of dose) by the thyroid reflected a diminution in the uptake of stable iodine. Reduction in radioiodine uptake is not necessarily accompanied by a reduction in absolute iodine uptake. Dissociation could arise from an increase in the total amount of circulating iodine which would cause a relative reduction in the proportion of radioactive atoms. Thus the number of radioactive atoms taken up by the thyroid may be diminished, while the number of stable iodine atoms may remain the same or even increase.

A further group of patients were treated with a combination of D-thyroxine and methylthiouracil, and the changes in the degree of exophthalmos were compared with a similar group of patients treated with methylthiouracil alone.

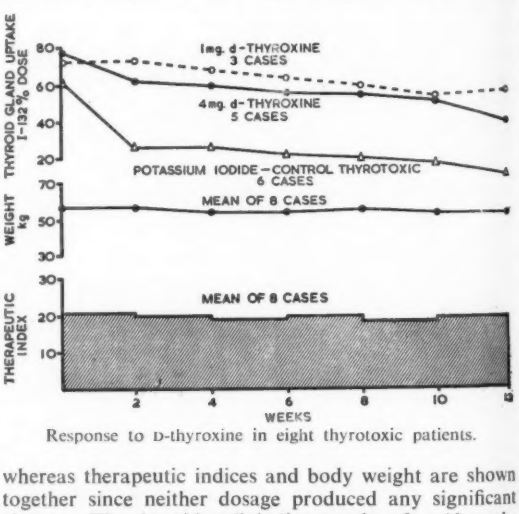
Materials and Methods

Four groups of thyrotoxic patients were studied. In each case the diagnosis was made on clinical grounds (Crooks *et al.*, 1959) and confirmed by both P.B.I. determinations (Farrell and Richmond, 1961) and radioiodine studies. Group 1 consisted of eight patients treated with D-thyroxine—three with 1 mg. and five with 4 mg. daily. Every two weeks measurements were made of body weight, therapeutic index (Crooks *et al.*, 1960), and the 2½-hour thyroid uptake of I-132. In three of these patients studies of stable iodine metabolism were carried out (Koutras *et al.*, 1960) before and after 12 weeks of treatment with 4 mg. of D-thyroxine daily. A control group of six thyrotoxic patients (group 2) were treated with equivalent amounts of potassium iodide (3.32 mg. of KI $\simeq$ 4 mg. of D-thyroxine), and estimations of A.I.U. were made before and at the end of 12 weeks of treatment. The A.I.U. is calculated as the product of the plasma inorganic iodine (P.I.I.) and the thyroid iodine clearance rate. The P.I.I. was estimated from measurements of the specific activity of the urinary iodine (Koutras *et al.*, 1960). Group 3 consisted of seven thyrotoxic patients treated with methylthiouracil 600 mg. daily for two weeks, followed by 300 mg. daily until euthyroid. Throughout the study these patients received 4 mg. of D-thyroxine daily. Every two weeks the therapeutic index and body weight were recorded and exophthalmometry was carried out (Zeiss–Hertel). Twelve thyrotoxic patients treated with methylthiouracil alone in the same doses acted as a control group (group 4).

Results

Group 1 (D-Thyroxine) and Group 2 (Potassium Iodide)

The results are shown in the Chart. The I-132 uptakes are shown separately for each dosage of D-thyroxine,



Response to D-thyroxine in eight thyrotoxic patients.

whereas therapeutic indices and body weight are shown together since neither dosage produced any significant change. The thyroid radioiodine uptake after 12 weeks of treatment decreased by a mean of 34% of the dose in those patients treated with 4 mg. daily. In those treated with 1 mg. daily the decrease was only 15%. The fall in uptake (49% at 12 weeks) was of greater magnitude and occurred more rapidly in the six cases treated with potassium iodide in amounts equivalent to 4 mg. of D-thyroxine (group 2). In contrast to the decreased radioiodine uptake, the stable iodine studies (Table I) showed that D-thyroxine caused no depression in the iodide-trapping mechanism of the thyroid. Thus, although the radioiodine uptake was found to be decreased, the stable iodine studies showed that this was not associated with a reduction in the A.I.U. (Table I). The mean P.I.I. in the three cases studied rose from 0.11 to 1.01 μg./100 ml., and this rise was not wholly compensated by the reduction in the thyroid iodine clearance

rate from 297 to 78 ml./min. Consequently the A.I.U. rose from a mean value of 19.8 to 32.2 μg./hour. The increase in P.I.I. can clearly be ascribed to liberation of free iodine from D-thyroxine. This was confirmed by the finding that there was an associated rise in the urinary iodine, which was almost entirely in the inorganic form.

TABLE I.—*Results of Stable Iodine Metabolism Studies*

	D-Thyroxine 4 mg. day (Mean of 3 Cases)		Pot. Iodide 3·32 mg. day (Mean of 5 Cases)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Thyroid iodine clearance (ml. /min.)	297·0	78·0	107·6	39·2
Plasma inorganic iodine (μg. /100 ml.)	0·11	1·01	0·18	4·58
Absolute iodine uptake (μg. /hr.)	19·8	32·2	11·6	51·0

Stable iodine metabolism in patients given equivalent amounts of iodine (group 2) followed a similar pattern (Table I). In this group the mean thyroid clearance fell from 107.6 to 39.2 ml./min., the P.I.I. rose from 0.18 to 4.58 μg./100 ml., and the A.I.U. rose from 11.6 to 51 μg./hour. The rise in the P.I.I. in patients treated with potassium iodide (+4.40 μg./100 ml.) was much larger than that in patients treated with D-thyroxine (+0.90 μg./100 ml.). This may be due to defective absorption or to biliary excretion of D-thyroxine, and probably explains the more rapid fall in thyroid uptake of radioiodine in those treated with iodide.

It is evident from the Chart that there was no clinical improvement over the 12-week period in the eight patients (group 1) receiving D-thyroxine. The therapeutic index showed no significant change, and there was a small decrease in the mean body weight. No individual patient showed worth-while clinical improvement.

Group 3 (Methylthiouracil + D-Thyroxine) and Group 4 (Methylthiouracil Only)

The changes in exophthalmos in millimetres are recorded in Table II, which shows the sum of the changes in both eyes for each case. The increase represents the difference between the control measurement and the measurement obtained when the patient became euthyroid. Both groups showed a significant increase in the degree of exophthalmos: the group treated with methylthiouracil plus D-thyroxine (2.1 ± 1.5 mm.) had no advantage over the control group (1.9 ± 1.7 mm.). One patient (not included in Table II) developed an acute protrusion of one eye while receiving treatment with D-thyroxine and methylthiouracil. The left eye protruded 11 mm. and the right 3 mm.

TABLE II.—*Effect of Treatment on the Exophthalmos in Thyrotoxic Patients*

Case No.	Methylthiouracil	Methylthiouracil and D-Thyroxine
1	3 mm.	5 mm.
2	1 ,,	2 ,,
3	1 ,,	1 ,,
4	1 ,,	3 ,,
5	4 ,,	2 ,,
6	2 ,,	0 ,,
7	−2 ,,	2 ,,
8	0 ,,	
9	3 ,,	
10	2 ,,	
11	4 ,,	
12	4 ,,	
Mean	1·9 ± 1·7	2·1 ± 1·5

The values represent the difference in exophthalmometry readings (sum of both eyes) before and after treatment. The mean and standard deviation for each group is shown.

Discussion

No improvement was noted in the clinical features of our thyrotoxic patients after treatment with D-thyroxine. However, an effect consistently found was the reduction of the radioiodine uptake by the thyroid, but stable iodine studies indicated that the absolute iodine uptake by the thyroid in μg./hour increased rather than decreased. This effect was similar to that found after the administration of potassium iodide in equivalent doses. The absence of significant amounts of organic iodine compounds in the urine and the rise in the level of the plasma inorganic iodine provides further evidence that the effect of D-thyroxine was due to the liberation of iodide. In thyrotoxic patients L-thyroxine does not suppress the uptake of radioactive iodine when given in doses of 0.2 to 0.3 mg. daily. D-Thyroxine, even in doses ten times as large, appears to be equally incapable of suppressing thyroid overactivity. There is thus no evidence that D-thyroxine specifically inhibited the pituitary–thyroid axis, and its effect can be entirely explained on the basis of an increase in the extrathyroidal iodine pool arising from the iodide liberated by the breakdown of the D-thyroxine in the tissues.

The exophthalmometry readings we report confirm that administration of antithyroid drugs is followed by a worsening of exophthalmos (Dobyns and Haines, 1946), possibly owing to an increase in the pituitary exophthalmogenic factor or factors. It is clear from Table II that D-thyroxine cannot prevent this increase in exophthalmos.

We conclude that D-thyroxine in the doses used is of no value in the treatment of thyrotoxicosis or of the associated exophthalmos.

Summary

No improvement in the clinical features of eight thyrotoxic patients was found after the administration of D-thyroxine. The increase in exophthalmos produced by antithyroid drug therapy was not prevented by concurrent D-thyroxine administration.

Studies of stable iodine metabolism showed no suppression of the iodide-trapping mechanism of the thyroid. The fall in thyroid uptake of radioiodine during treatment with D-thyroxine was shown to be due to liberation of iodide.

It is concluded that D-thyroxine in the dose range used is of no value in the treatment of thyrotoxicosis or of the associated exophthalmos.

We thank Professor E. J. Wayne for permission to treat these cases and for his helpful advice and encouragement. We are indebted to Dr. R. D. Hunter for carrying out the exophthalmometry readings. Glaxo Laboratories Ltd. generously supplied all the D-thyroxine and potassium iodide tablets used. This study was supported in part by grants from the Secretary of State for Scotland on the recommendation of the Advisory Committee of Medical Research, and from the Medical Research Council.

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COMPARISON OF THE INSULIN AND ELECTRICAL STIMULATION TESTS FOR COMPLETENESS OF VAGOTOMY

BY

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Vagotomy combined with a drainage procedure or limited gastrectomy has an established place in the surgical treatment of duodenal ulcer. One of the problems associated with this operation is the difficulty of achieving a complete vagotomy in every case. Thus Camp and Dragstedt (1948) reported incomplete vagotomy in 10% of their cases. Holt and Robinson (1955) and Walters and Mobley (1957) had 12% and 18% respectively of incomplete vagotomies, and a similar incidence has been reported by other workers.

The insulin test introduced by Hollander (1946, 1948) has been widely used to assess the completeness of vagotomy, but it suffers from the drawback that it cannot be employed until after the operation is finished. In an attempt to provide information during operation, Burge and Vane (1958) introduced an electrical stimulation test. Electrodes were placed around the lower oesophagus and the intragastric pressure was recorded during stimulation. A rise in pressure was taken to indicate the presence of intact vagal fibres. The absence of any rise during stimulation was regarded as evidence of a complete vagotomy.

The present investigation was undertaken in order to compare the results of these two tests in a series of patients.

Methods

Twenty-five patients undergoing vagotomy and anterior pylorectomy for chronic duodenal ulcer were studied. In each case the insulin test was performed before and after operation, and the electrical stimulation test was applied during the operation. The tests were also employed in one patient who was undergoing a second operation after an incomplete vagotomy.

Insulin Test

The patient was given no food after 4 p.m. on the day before the test, and no fluids after midnight. On the morning of the test a Ryle tube was passed into the stomach. The fasting contents were completely aspirated, and immediately thereafter a sample of blood was taken for blood-sugar estimation. 20 units of soluble insulin were then administered intravenously, and the gastric contents were completely aspirated at 15-minute intervals for the succeeding two and a half hours. The blood-sugar estimation was repeated 30 and 60 minutes after the beginning of the test. All samples of gastric contents were titrated for free and total acid, and the results expressed as millilitres of N/10 HCl per 100 ml. of gastric contents (hereafter referred to as "units").

In interpreting the result of the test the somewhat rigid criteria laid down by Hollander (1948) were adopted. The test was considered positive—that is, indicative of incomplete vagotomy—if, after adequate hypoglycaemia, one or more points on the free-acidity curve were elevated by more than 20 units above the resting value. Where the resting juice contained no free acid, a rise of 10 units was regarded as significant. The only departure from Hollander's criteria was when the maximum values on the free-acidity curve were reached more than two hours after the beginning of the test. These tests were considered negative for reasons which are discussed later.

Electrical Stimulation Test

In performing this test the original method of Burge and Vane (1958) was slightly modified in detail. Premedication of the patients with opiates or atropine was avoided, but promethazine hydrochloride in a dose of 50 mg. was found not to interfere with the test, and was given to the later cases. Anaesthesia was induced with thiopentone and maintained with nitrous oxide and oxygen, and the relaxants employed were suxamethonium chloride followed by D-tubocurarine.

A left paramedian incision was used in every case, and after mobilization of the lower oesophagus the Burge electrode was applied before attempting to divide the vagi. After passing the cuffed gastric tube and occluding the pyloric antrum with a light clamp, the stomach was distended with air and the intragastric pressure recorded on a water manometer as described by Burge (1960). Each quadrant was stimulated in turn, using square wave pulses of frequency 25 per second and duration 1 msec. This frequency and duration was found to give a maximal response. Various voltages were used, but 30 volts was found adequate in most cases. Note was taken of the quadrants in which stimulation had caused a rise in intragastric pressure. A rise in pressure of 1 cm. or more of water was regarded as significant.

The electrode was then removed and the vagotomy performed. Both main trunks were divided, a portion of each was excised and the ends were ligated with linen thread. No attempt was made to spare any branch of either nerve. In addition, a careful search was made for any smaller strands of nerve lying on the lower oesophagus, and these were divided. When no further fibres could be detected the stimulation test was repeated.

The operations were completed by performing an anterior pylorectomy. The anterior half of the pyloric sphincter was excised with closure in the transverse axis as described by Beattie (1950).

Results

Vagotomy and Anterior Pylorectomy Cases.—In each of these 25 patients the pre-operative insulin test was strongly positive, and the maximum values on the free-acid curve often exceeded 100 units. When the electrical stimulation test was applied before the vagotomy, a positive response to stimulation in some or all quadrants of the electrode was obtained in 22 of the patients. In the remaining three no rise in pressure could be recorded in response to stimulation of any quadrant, in spite of variations in the voltage and frequency of pulses. The apparatus was carefully checked and found to be in order, and no explanation is offered to account for the failure in these three cases, in which the test had to be abandoned. After performing the vagotomy, the stimulation test was repeated in the 22 patients in whom a positive response had previously been obtained. In no case was there any rise in pressure in response to stimulation of any quadrant. The insulin test was repeated, usually between the seventh and twelfth post-operative days. In 22 cases the result was negative, indicating complete vagotomy; but a positive result was obtained in three cases. Two of these were

cases in which the electrical stimulation test had indicated complete vagotomy, and the third was in one of the patients whose stimulation test had been abandoned. These results are summarized in the Table.

Results

	Insulin Test	
	Positive (Incomplete Vagotomy)	Negative (Complete Vagotomy)
Electrical stimulation test negative (presumed complete vagotomy)	2 cases	20 cases
Electrical stimulation test unsuccessful ..	1 case	2 cases
Total ..	3 cases	22 cases

Incomplete Vagotomies.—Graphs of the insulin test results in the three patients with incomplete vagotomies are reproduced in Fig. 1. In Case 1 the electrical test before vagotomy gave a pressure rise with stimulation of the right anterior and right posterior quadrants, but in Case 2 there was a rise with stimulation of the right posterior quadrant only. In both cases there was no pressure rise after vagotomy. Case 3 was the patient in whom the test gave no pressure rise before vagotomy. In all three patients both main vagal trunks were identified and divided, and in each case several smaller strands of tissue presumed to be nerve were also severed.

Repeat-Vagotomy Case.—This patient had undergone vagotomy and posterior gastro-enterostomy eight years previously. Five years after the operation he suffered a recurrence of ulcer symptoms which persisted, and the insulin test was positive (Fig. 2). A further operation was undertaken in the hope of completing the vagotomy. After mobilization of the lower oesophagus a small nerve strand was seen running along the right border of the oesophagus. Before dividing this nerve, the electrical stimulation test was performed. In addition to the clamp across the pyloric antrum a light clamp was placed across the gastro-enterostomy stoma in order to allow distension of the stomach. Stimulation of the right posterior quadrant gave a rise in pressure of 0.5 cm. of water. The nerve was then divided and the test repeated. No response to stimulation in any quadrant was obtained. The operation was completed by separation of the gastro-enterostomy and the performance of an anterior pylorectomy. The post-operative insulin test was negative (Fig. 3), indicating that the vagotomy was now complete.

Discussion

The investigation has revealed a discrepancy between the results of these tests in three patients, and it is therefore appropriate to consider the possible fallacies in the interpretation of each test.

Insulin Test

The significance of a negative or positive response to the insulin test is discussed in detail by Hollander (1948) and by Weinstein, Hollander, Lauber, and Colp (1950). They consider that a true negative response after adequate hypoglycaemia (blood sugar 50 mg. or less per 100 ml.) indicates complete interruption of all secretory nerves to the stomach. A false-negative result may occur in patients who have been subjected to partial gastrectomy or gastro-enterostomy. In these cases there may be loss of acid through the stoma, or neutralization by regurgitation of alkaline bile and pancreatic juice into the stomach. This objection does not apply to quite the same extent after anterior pylorectomy or pyloroplasty. False-negative results may also occur in patients with achlorhydria, but no such case is included in the present series. Failure to place the tip of the Ryle tube accurately in the stomach can also cause false-negative results. For these reasons a single negative response to the insulin test cannot be taken as certain evidence of complete vagotomy. However, a positive response was regarded by Hollander as a definite indication of the persistence of some secretory nerves to the stomach.

Subsequent experimental work in monkeys (French, Longmire, Porter, and Movius, 1953) demonstrated that insulin hypoglycaemia exerts its effects on gastric secretion by two separate mechanisms. An early rise in secretion is brought about by excitation of the anterior hypothalamus and is mediated by way of the vagus nerves. A second and later phase occurs after a delay of about two hours, and is due to a hormonal mechanism involving the pituitary and adrenal glands. This dual response to hypoglycaemia was later demonstrated in humans (Stempien, French, Dagradi, Movius, and Porter, 1958), and 50 patients who had undergone vagotomy and pyloroplasty were studied. It was shown that complete vagotomy abolished both phases of secretion in most cases. In a minority, however, only the early (vagal) phase was abolished and the delayed (pituitary-adrenal) phase persisted. Patients with incomplete vagotomy had a persistence of secretion in the early phase.

In the present investigation the insulin tests were not continued beyond two and a half hours, but a number of the pre-operative tests show a second rise in acidity occurring after two hours. A typical example is shown in Fig. 4, in which the acidity curve represents a summation of the two separate responses.

Three patients in the present series gave a response in the post-operative insulin test in which the maximum values on the free-acidity curve were reached two hours or more after the beginning of the test. In each of these cases the maximum values for the nervous phase in the pre-operative test had been earlier, and there had been a steep rise in the acid curves within 30 minutes of the beginning of the test (Fig. 5). It is concluded that the response in these three patients is due to the hormonal phase, and that the vagotomies should not be regarded as incomplete.

In the three patients regarded as having incomplete vagotomies (Fig. 1) the maximum values on the free-acidity curve in the post-operative test coincide in time with the maximum values reached in the pre-operative test. (The difference does not exceed 15 minutes in any case.) In the light of the evidence already cited, it must be presumed that these responses are due to the nervous phase, and indicate the persistence of some secretory nerve fibres.

Electrical Stimulation Test

It has been shown that patients in whom the electrical stimulation test gives no response after vagotomy may yet have an incomplete vagotomy as judged by the insulin test. There are two possible explanations for this.

1. The persisting fibres may lie within the ring electrode but fail to respond to stimulation. This could theoretically occur if a branch contained secretomotor fibres but no fibres to smooth muscle. Alternatively, the test may not

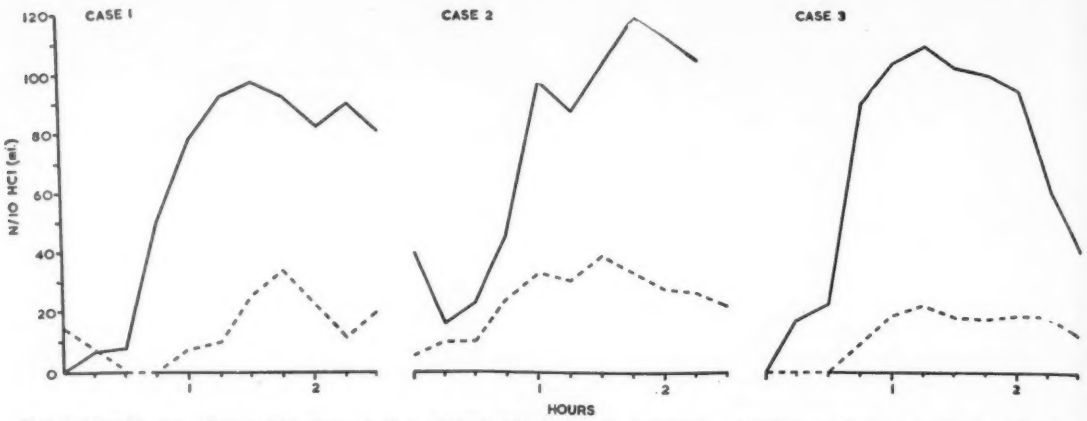

FIG. 1.—Insulin test. Free-acidity curves in three patients with incomplete vagotomy Continuous line=pre-operative. Broken line=post-operative.

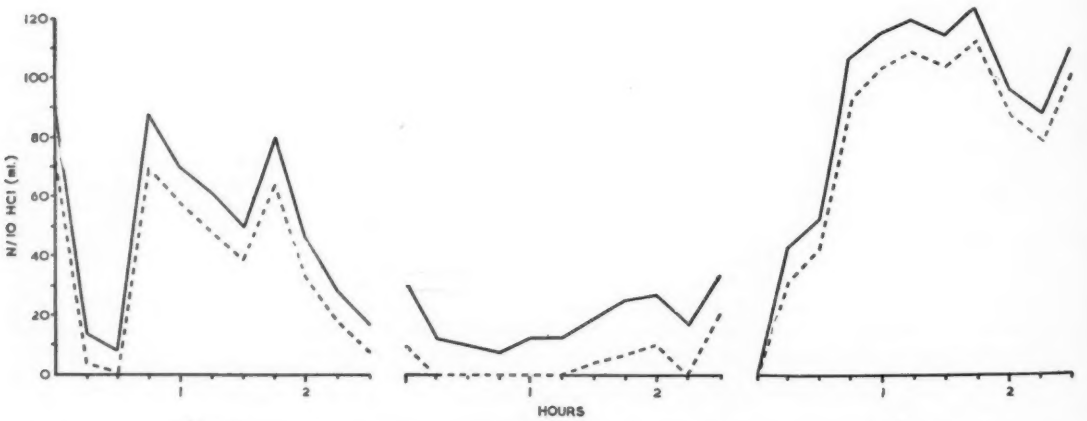

FIG. 2 FIG. 3 FIG. 4

FIG. 2.—Insulin test in patient requiring second operation for incomplete vagotomy. Continuous line=total acid. Broken line=free acid. FIG. 3.—Insulin test in same patient as Fig. 2, after completion of vagotomy. FIG. 4.—Insulin test showing dual response to hypoglycaemia. Continuous line=total acid. Broken line=free acid.

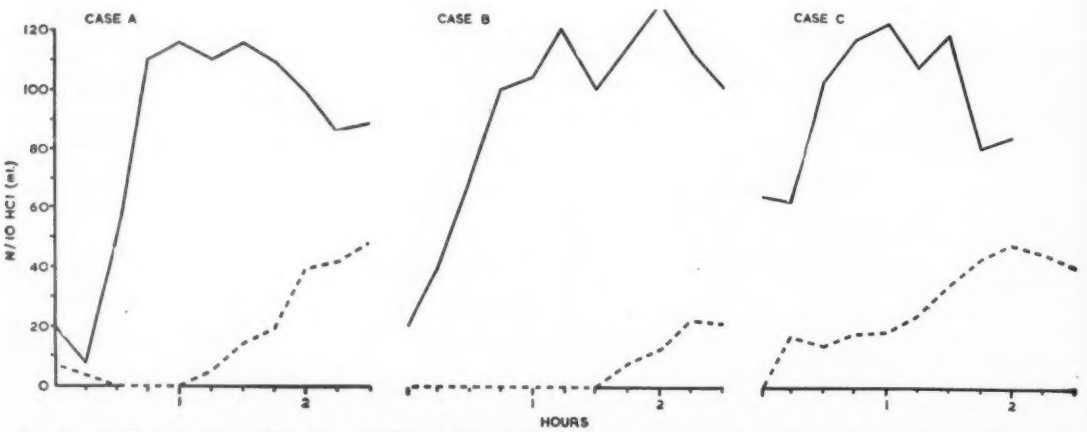

FIG. 5.—Insulin test. Free-acidity curves in three patients showing late response in post-operative test. Continuous line=pre-operative. Broken line=post-operative.

be sensitive enough to detect the smaller branches. Burge and Vane (1958) showed that stimulation of very small branches can cause a pressure response, and the same phenomenon has been observed in some of the patients in the present series. However, in several other cases branches were seen which did not give a response to stimulation; and in three patients there was no response even before the vagotomy had been performed. Perhaps there is some other variable factor affecting the responsiveness of the stomach to vagal stimulation.

2. The persisting fibres may not lie within the ring electrode. Stempien and Weinberg (1953) reported a series of patients undergoing further operations for incomplete vagotomy. In four of them they found the main posterior vagus intact. In such a case the surgeon had presumably failed to locate the nerve in mobilizing the oesophagus, and had he applied the Burge electrode he would have left the nerve outside its grasp. If a main trunk can escape in this way, so presumably can its branches.

The anatomy of the vagi has been extensively investigated. Walters, Neibling, Bradley, Small, and Wilson (1947) found the branches lying on the lower oesophagus in an accessible position in 92% of cases. In the remaining 8% the oesophageal plexus divided into numerous branches. Some passed through the hiatus, but others spread laterally into the thorax, and may have entered the abdomen at a distance from the oesophagus. Chamberlin and Winship (1947) also found the anterior and posterior nerve "complexes" in abnormal positions in 12 and 18% of cases respectively. It may well be that in these "abnormal" cases some fibres would not be included within the electrode and would thus escape detection.

There remains the possibility that some secretory fibres may reach the stomach via the splanchnic nerves. Malméjac and Donnet (1940) demonstrated cholinergic fibres to the stomach in the splanchnic nerves of dogs, and if the same is true in humans, then they might participate in the secretory response to hypoglycaemia and account for some of the "incomplete vagotomies."

Of these two explanations for the discrepancy between the results of the insulin and electrical stimulation tests, the second probably accounts for the incomplete vagotomies. The fact that even the most experienced vagotomists perform an incomplete operation in slightly more than 10% of cases suggests that the missing fibres are not to be found in the area which is normally searched, and which would be included in the electrode during the stimulation test.

Conclusions

It remains to consider what is the place of these two tests in clinical practice.

The pre-operative insulin test may be of some help in diagnosis. If there is not a marked rise in acid secretion in response to hypoglycaemia the diagnosis of duodenal ulcer is unlikely to be correct.

Routine employment of the insulin test post-operatively will not help in the management of the individual patient, but it provides the surgeon with a measure of his skill in performing complete vagotomies, and is useful for research purposes. The insulin test is of real value in a patient with persistent or recurrent symptoms after vagotomy, and in whom further surgery is contemplated. If the test is positive, an attempt may be made to complete the vagotomy.

Clearly, it would be of great value to have a test which could detect an incomplete vagotomy at the time of operation and would allow the surgeon to make a further search for the remaining branches. However, routine employment of the electrical stimulation test in 25 patients has not prevented a 12% incidence of incomplete vagotomy as judged by the insulin test. Moreover, the results in this series would have been the same without the test, because in no case was there a positive response to stimulation after division of all the branches which could be found at the first attempt.

In the patient who was undergoing a second operation after incomplete vagotomy, the persisting branch was located before performing the test and its presence was confirmed by the test. It cannot be denied that had the test been performed at the time of the first operation the vagotomy might have been made complete. However, this operation had been done through a right paramedian incision, which gives poor access to the lower oesophagus. If the access had been good enough to allow performance of the test, the nerve might well have been seen or felt at the time.

There is no doubt that the electrical stimulation test can detect persisting vagal branches on the lower oesophagus, and that these account for some cases of incomplete vagotomy. It is suggested that there are other cases in which the persisting nerves are not in a position to be stimulated by the electrode or do not respond to stimulation. It may still be argued that the test will detect some incomplete vagotomies, and for this reason should be used routinely.

There are, however, some minor drawbacks to the test. The operation is prolonged by about 15 to 20 minutes, which does not usually matter. The omission of atropine or hyoscine from the premedication is a more serious objection. In many of the cases quite large volumes of secretion have required to be aspirated from the bronchi, and several patients developed troublesome post-operative chest infections. The impression was gained that these chest complications were more common and more severe than in patients receiving the usual premedication, although the total numbers are insufficient for statistical comparison. However, it would seem wise to avoid the test in patients known to have bronchopulmonary disease.

In the present investigation the electrical stimulation test has not proved to be of great practical value. The incidence of incomplete vagotomy has been of the same order as that achieved without the test, and in the light of this experience the employment of the test as a routine measure in clinical practice does not seem justified.

The operation of vagotomy, performed with scrupulous care and involving a most careful search for branches on the lower oesophagus, still fails in just over 10% of cases to interrupt all secretory nerves to the stomach. This percentage is not reduced by the electrical stimulation test, and the suggested explanation is that the persisting fibres are at some distance from the oesophagus. If this is so, the time devoted to performing the test might be better spent in searching for nerves.

Summary

The insulin test was performed before and after operation and the electrical stimulation test was applied during operation in 25 patients undergoing vagotomy and anterior pylorectomy, and in one patient undergoing a second operation after incomplete vagotomy.

In the vagotomy and pylorectomy series the electrical stimulation test indicated complete vagotomy in 22 cases, and failed to provide information in three cases.

The post-operative insulin test was positive, indicating incomplete vagotomy, in three cases. Two of these were patients in whom the electrical stimulation test had indicated the vagotomy to be complete.

During the operation undertaken for incomplete vagotomy a persisting nerve branch was located, and its presence confirmed by the electrical stimulation test. Division of this branch rendered the vagotomy complete as judged by the insulin test.

A single negative response to the insulin test does not necessarily indicate a complete vagotomy, but a positive response with maximum values on the free-acidity curve less than two hours after the beginning of the test is evidence of the persistence of some secretory nerves to the stomach.

Two explanations are offered for the occurrence of incomplete vagotomies where the electrical stimulation test had indicated them to be complete. Either the persisting fibres lie within the ring electrode but fail to respond to stimulation, or they are outside the grasp of the electrode at a distance from the oesophagus. The latter is considered the more likely explanation.

The insulin test is useful in diagnosis and as a measure of the surgeon's skill in performing vagotomy. It is valuable in relapsed patients after vagotomy when further surgery is contemplated.

Employment of the electrical stimulation test in this series did not reduce the incidence of incomplete vagotomy, and its use as a routine measure does not appear to be justified.

I thank Mr. R. L. Holt for his encouragement and advice in this work, and for permission to study the patients, and Mr. H. W. Burge for kindly demonstrating to me the technique of his test. I am also grateful to the various anaesthetists who have helped me with the electrical stimulation tests, and particularly to Dr. J. Greenan and Dr. A. Melvin.

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"The size of the programme of special school building has risen steadily over the years until now work amounting to about £2¼m. is authorized each year. In ten years over 21,000 extra special school places have been provided, an increase of more than 50%, and almost any handicapped child, unless he is educationally subnormal or maladjusted, can now be placed in a special school in quite a short time. . . . The big problem now is the persistent shortage of places for educationally subnormal and maladjusted children. Over 10,000 new places for these children are in the pipeline, and our major effort for the next few years must be to provide the rest of the places still needed for them." (Mr. Kenneth Thompson, Parliamentary Secretary to the Ministry of Education.)

INTUBATED JEJUNOSTOMY FOR RECURRENT SMALL-BOWEL OBSTRUCTION DUE TO PERITONITIS

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Post-operative distension in patients recovering from generalized peritonitis is normally due to paralytic ileus. Sometimes it is otherwise caused, and when loud obstructive sounds are heard on auscultation the decision to reoperate is an unpleasant one to have to make, for, as experience shows, the cause of the obstruction is not an isolated band which could easily be found and divided, but a complex and multiple system of interileal adhesions containing loculated pus. To have to deal with these in a patient already depleted by his main illness, from which he had only just begun to recover, is a trial of skill and judgment which no surgeon welcomes; for recurrence is common, and with each episode the gravity of the situation deepens. There is still a high mortality inherent in this difficult situation, for whose correction orthodox measures must be admitted to have failed. If a means could be found of tiding the patient over the final stages of the resolution of his abdominal sepsis—for, as we know, a nearly normal abdomen can be regained within a matter of weeks—the vicious circle of operation→obstruction→operation could very likely be broken and a natural recovery should then ensue.

During the past year we have had three such cases, each subsequent to a perforation of the lower bowel, and we have found that more can be done than to break down the adhesions at the principal point of obstruction.

Technique

The abdomen is reopened through the original incision, and the most distended loop of bowel is opened, packs having been placed about it; a cannulated sucker is held ready to catch the gush of gas and fluid from the small initial hole. The sucker is then advanced up the small bowel, emptying it and threading the collapsed, oedematous, inflamed gut on to the cannula. One or even 2 litres of soupy material collects into the sucker bottle. A second enterostomy may be required if the bulk of the collapsed bowel on the sucker will not allow the operator to advance it up the full length of the small bowel. When this has been done, and the abdomen by this time has become much less tense, a small left subcostal jejunostomy is made comfortably close to the duodeno-jejunal flexure, and into it is passed a Miller–Abbott tube, which is then brought down, as the sucker is withdrawn, so that its tip comes to lie in the low ileum, near the point of obstruction. The enterostomies and jejunostomy are then closed. We normally close the abdomen as for wound rupture, with thick stainless-steel wire.

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Post-operatively, low-pressure suction is applied to the Miller–Abbott tube for several days, even after the need for intravenous feeding has passed. Large quantities of gas are produced, and a variable amount of fluid. When this becomes thicker and more difficult to aspirate, the patient generally passes a loose spontaneous bowel motion, and recovery may be expected. Three cases in which this method was found effective are described.

Case Reports

Case 1.—A labourer aged 23 was admitted to hospital with a history of 24 hours' abdominal pain and the signs of generalized peritonitis. At operation the abdomen was found to contain thick green offensive pus, and a perforated gangrenous appendix was removed. On the third post-operative day he developed a gross, painful distension with vomiting and increased bowel sounds, and a second operation was performed. An obstructed loop of ileum was freed, and proximal decompression with a sucker was carried out. Ten days later he again presented the picture of acute small-gut obstruction. A swallowed Miller–Abbott tube could not be entered into the jejunum, so a third operation was undertaken, with the method described in mind. The state of the abdomen was far worse than before, with widespread adhesions and many abscesses. The method described was used for the first time and continuous suction was applied. He was able to resume oral feeding on the seventh day. Eight days later the tube was removed. The jejunostomy drained for a few days, but the patient's recovery continued otherwise uneventfully and he was working again as a labourer seven weeks after his discharge from hospital.

Case 2.—A man of 83 was admitted to hospital with a three-day history of left-sided lower abdominal pain, and a clinical diagnosis of acute diverticulitis was made. Next day his pain increased, and abdominal rigidity and tenderness quickly became generalized. At operation the cause for the peritonitis was found to be a large leaking peri-sigmoid abscess, which centred on a perforation of the apex of the sigmoid loop. A 6-in. (15-cm.) segment of the colon with the perforation at its centre was resected, and the colon was anastomosed. He made an excellent recovery until on the tenth day he developed intestinal obstruction, which did not improve with several hours' gastric aspiration and intravenous fluid replacement. Operation was therefore undertaken, and a loop of small bowel was found adherent to the under side of the incision and to the anastomosis. Many other coils in the vicinity were closely adherent with fibro-fibrinous adhesions. The procedure described was carried out: the balloon of the Miller–Abbott tube in this case could be made to reach the ileo-caecal valve. After nine days' suction the patient had regained his bowel function and the tube was removed. He did experience a short bout of obstructive symptoms five days later, but his recovery quickly resumed and he remained well four months later. The pathological report on the sigmoid colon showed the perforation to have occurred not at the site of an acute diverticulitis but in a small adenocarcinoma.

Case 3.—A man of 67 was found at operation to have a gangrenous appendix, and his post-operative course after its removal was stormy. He developed increasing distension despite gastric aspiration and intravenous fluid replacement, and on the eighth post-operative day his general condition began to deteriorate for the first time. He was by then very distended indeed, so operation was undertaken and many adherent ileal loops were found in the right iliac fossa, these being the cause of the obstruction. They were freed, and an intubated jejunostomy was made as described, the patient doing well. In this case a recurrent bout of obstruction developed 11 days after the first, the Miller–Abbott tube having been removed three days before. However, the jejunostomy had not yet closed, so that the tube could be reinserted without difficulty and soon was carried along to approximately half its length by intestinal peristalsis. Three days later it was removed, and before long the jejunostomy sealed itself off. The patient made a good recovery, and remained well three months after operation.

Discussion

In the U.S.A. intestinal intubation has for many years been routine in the management of recurrent obstruction; but in this country it has never found much favour. The Miller–Abbott tube is generally regarded as too difficult to pass, and its main potential danger is that its use may mask the need for open operation, as, for example, in strangulation obstruction. We thought that these two objections would be overcome if the tube could be passed at operation, and our early experiences seem to justify further trial of the method.

The problem of recurrent intestinal obstruction has not yet been solved. So much is left to chance by the standard operation of freeing the adhesions responsible for the current episode and trusting that they will not re-form in a similar manner. It is not surprising that a policy of conservatism in such cases has been generally adopted. A false sense of security may be engendered by the institution of gastric aspiration (often ineffective) and intravenous fluid replacement (generally governed by day-old blood chemical estimations, rather than consideration of fluid losses: which indeed may be internal and therefore hidden and impossible to assess). Cooke (1958) has emphasized the need for a return to more active management by early operation in acute intestinal obstruction. Logically, this should apply also to recurrent cases, and if something more than temporary correction could be achieved in these patients a difficult problem would be solved.

Noble (1937) suggested that "controlled adhesions" produced by suturing the whole small gut in regular folds might be safer than accepting the risk of the gut returning to its confined and angulated state. Later he wrote that he had never seen a case of intestinal obstruction after this operation (Noble, 1945). Lord (1951) has reported favourably on the Noble "plication operation." In 9 out of 11 patients the result was highly satisfactory. Nevertheless, it seems that the prospect of adding such an operation to the burden of the main intervention has prevented any general adoption of it. A simpler alternative was suggested by White (1956), who used a long intestinal tube, of semi-rigid consistency, as a means of intraluminal splinting of the freed bowel for the purpose of controlling the disposition of the post-operative adhesions, much as Noble did with his plication sutures. White either intubated the bowel before operation through the nose, or at operation, retrogradely, via a caecostomy. Twelve out of 14 patients treated thus did well according to a follow-up survey, between one and six years later.

More recently Heydinger *et al.* (1960) reported their experimental findings in a comparative study of plication and intubation in dogs, and a clinical experience of 10 patients with operative intubation for recurrent obstruction. They found that in the dogs either procedure produced a regular and well-functioning disposition of the small bowel, while all of the 10 patients in whom intraluminal splinting was used did well. They emphasize the advantages in time-saving with the tube method.

We have not yet adopted this regime for patients with multiple recurrences and a history of much surgery. Often these patients are socially unreliable, and many are drug addicts. We do intend to try it, however, if

forced to abandon conservatism in such a case; for, as both Noble and White have reported, some patients even of this unfavourable type have been completely relieved. At present, however, we are reasonably convinced that the intubated jejunostomy, perhaps by its decompression function, or perhaps by the merit of providing a more orderly pattern for the intestine, is a most effective means of dealing with recurrent post-operative obstruction where the cause is recent peritonitis.

Summary

Many cases of recurrent small-intestinal obstruction are not at present treated adequately.

Intubation of the whole small bowel at operation, via a jejunostomy, after suction decompression, proved to be successful in the treatment of the three cases described.

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REPAIR OF CARDIAC DEFECT IN PATIENT WITH EHLERS–DANLOS SYNDROME AND DEFICIENCY OF HAGEMAN FACTOR

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Congenital defects of the cardiac septa usually have no known cause, but an incidence of 20–30% in arachnodactyly (Marfan syndrome) and mongolism has been observed (Wood, 1956). Congenital heart disease of all kinds is apparently rare in patients with Ehlers–Danlos syndrome, a hereditary disorder of connective tissue. We have found only one report of such an association, in which the patient had tetralogy of Fallot (Wallach and Burkhart, 1950).

The essential manifestations of the Ehlers–Danlos syndrome are friability of the skin and blood-vessels, undue mobility of the joints, and excessive distensibility and elasticity of the skin. The syndrome is transmitted as a Mendelian dominant character and has often been observed together with other anomalies (Johnson and Falls, 1949; Summer, 1956; Macfarlane, 1959; Zaidi, 1959). McKusick (1959) has stressed how little knowledge we have of the visceral abnormalities which may occur in this condition.

Hageman trait is a rare defect of blood-clotting which does not cause abnormal bleeding, despite a severe coagulation defect which is detectable in laboratory tests (Ratnoff and Margolius, 1957).

The occurrence of partial persistent atrio-ventricular canal in a patient with both Ehlers–Danlos syndrome and deficiency of Hageman factor must therefore be exceedingly rare. Such a combination and relevant observations are reported in the following case.

Case Report

A boy aged 11 years had been regarded as normal until the age of 8 years, when a heart murmur was detected by the school medical officer and he was referred to the cardio-thoracic unit of the Alfred Hospital. He had the clinical features of an atrial septal defect with left axis deviation in the electrocardiogram, suggesting the diagnosis of partial persistent atrio-ventricular canal. Two and a half years later his poor muscular development was noted, and he had developed symptoms of exertional dyspnoea. Cardiac catheterization and femoral-artery puncture performed without incident indicated a left-to-right shunt at both the atrial and ventricular levels, and the pulmonary blood flow to be four times greater than the systemic flow. The original diagnosis was retained, and he was admitted to hospital for repair of the defect three years after the first examination.

The patient, his mother, and at least 15 of her relatives (Fig. 1) had experienced abnormally easy bruising; the size

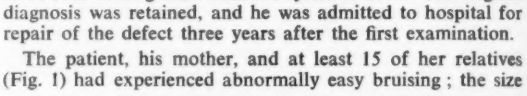

FIG. 1.—Part of family tree of the patient, who is shown by the arrow. Died indicates died in infancy.

of the ecchymoses was small (up to 4 cm. diameter). All had experienced large lacerations (5 cm. or more in length) requiring suturing of the knees and lower legs after minor traumata. Healing occurred without difficulty but resulted in broad scars of tissue-paper thinness. Excessive bleeding never occurred from these wounds or from accidental incised wounds. The affected relatives and the patient had not suffered from bleeding from mucous membranes, or into the joints and deeper tissues or from the uterus. The skin over the knees and elbows of the patient and his mother was unduly extensible; it could be pulled out to 4–5 cm. and felt elastic. On release the skin immediately resumed its normal contour. Apart from numerous large scars over the knees, the skin felt and appeared normal. Their wrist- and finger-joints were excessively mobile, so that they could be bent dorsally and almost touch the forearm. These features indicated that the patient had the Ehlers–Danlos syndrome of a mild-to-moderate severity.

Pre-operative blood examinations gave the following results: haemoglobin, 14.8 g./100 ml.; white cells, 9,000/c.mm.; platelets, 280,000/c.mm. Skin bleeding-time and capillary resistance tests were normal. Blood-clotting studies are given in Tables I and II.

From the coagulation tests it is seen that the blood-clotting time and the partial thromboplastin time were prolonged. Prothrombin time was normal. From these results it seems that there was a defect in the early stages of blood coagulation. Thromboplastin generation tests

showed only abnormal results when both $BaSO_4$-treated plasma and serum from the patient's blood were used. When one of these components was obtained from normal blood the results were normal. Tests using the partial thromboplastin time were used to establish the coagulation defect, and the results are given in Table II.

The results in Table II show that the clotting-time of the patient's plasma could not be reduced by the addition of suspensions of kaolin or bentonite, but was reduced to normal figures by the addition of normal serum and adsorbed plasma, and serum from a patient with complete Factor IX deficiency (haemophilia-B). These results are characteristic of a coagulation defect due to lack of Hageman factor or P.T.A. (plasma thromboplastin antecedent) (Margolis, 1958). Addition of the patient's plasma to that from a patient (S.) with Hageman-factor deficiency showed that the patient's plasma had only little effect in correcting the Hageman-factor deficiency. This establishes the diagnosis of Hageman-factor deficiency in the present patient. Assuming that S. plasma had a complete deficiency of Hageman factor, our patient had in his plasma not more than 1–2% Hageman-factor activity.

Operation was performed, using total body perfusion with a Kay–Cross disk oxygenator. It was observed that the septal leaflets of both ventral and tricuspid valves were cleft and that there was a low atrial septal defect 3 cm. in diameter. No ventricular septal defect was found. The clefts in the valves were closed with interrupted sutures, and a plastic prosthesis was sewn into the atrial septal defect. The patient (weight 28 kg., height 145 cm., body area 1.08 sq. m.) received 6,000 units of heparin intravenously and 5,400 ml. of heparinized blood (4 units heparin/ml.) during the extracorporeal circulation. The by-pass lasted 40 minutes. The observed heparin concentrations in the patient's blood are given in Fig. 2. It is seen that approximately 100 minutes after the protamine sulphate injection the patient's blood was free of heparin, and coagulation tests, including fibrinogen determination and platelet count (185,000/c.mm.), were normal. The total drainage from the chest in the post-operative period was 290 ml. This figure is in the low range for this type of surgery.

The gradual disappearance of Hageman-factor activity from the patient's blood was determined by the partial thromboplastin-time technique, and results are given in Fig. 3. It is seen that the disappearance of Hageman factor from the patient's circulation followed an exponential curve and the half-life of Hageman factor was approximately two days. The chest wound healed in normal time, but the scar was somewhat broader than normal. Nine months after the operation he won the following events: 80 yards sprint, the hop, step, and jump, and the broad jump, and he became senior athletic champion at the primary school he was attending.

TABLE I.—*Coagulation Data of Venous Blood*

	Patient	Normal
Blood-clotting time (mins.), glass 35° C.	27–54	12–20
,, ,, ,, ,, silicone 35° C.	120–160	40–80
Clot retraction	Normal	—
Partial thromboplastin time (secs.) ..	390–600	75–85
Prothrombin time (secs.)	13	12–13
Platelet count/c.mm.	150,000	100,000–300,000
Thromboplastin generation (secs.) with:		
Patient's Ba-plasma and patient's serum	25–28	10–11
,, ,, ,, normal ,,	10	—
Normal ,, ,, patient's ,,	10	—

TABLE II.—*Partial Thromboplastin Time (secs.) of Plasma**

Patient's plasma + NaCl	390–600
,, ,, + 5 mg. kaolin; 0·8 mg. bentonite ..	375–510; 350
,, ,, + normal Ba-plasma	150
,, ,, + ,, serum	82
,, ,, + $Al(OH)_3$-treated normal serum ..	110–150
,, ,, + haemophilia-B plasma	166
,, ,, + ,, serum	177
Hageman-deficient plasma (S.)	900
,, ,, + 50% patient's plasma ..	520

* 0·2 ml. of citrated plasma + 0·1 ml. of phospholipid suspension + 0·05-ml. additions, as indicated, were incubated at 35° C. and 0·2 ml. of 0·025 M calcium chloride added.

Discussion

Cardiac surgery has been carried out successfully in patients with various anomalies associated with their cardiac defect. The Ehlers–Danlos syndrome might be thought to be a condition in which surgery could result in unusual difficulties due to friability of the tissue, and the thin and weak scars which result from wounds. A number of surgical procedures have been carried out on these patients. These include amputation of a leg (Johnson and Falls, 1949), lens extraction (Thomas *et al.*, 1954), appendicectomy (Packer and Blades, 1954), bone grafting (Saemundsson, 1956), skin grafting (Ricketson, 1957), and thoracoplasty (Ross and Dooneief, 1957). Difficulties sometimes encountered during operation were caused by the friability of the tissues, which allowed skin sutures to tear out and haemostats to drop off. Slow healing, which sometimes occurred, resulted in herniation of the iris and failure of skin grafts to take, and might have been the cause for non-union in the case reported by Saemundsson. Excessive bleeding after tonsillectomy in a patient has been referred to by Johnson and Falls (1949). Operation scars have been stated to become broad along almost their whole length. In spite of the foregoing, absence of surgical difficulties in a patient with Ehlers–Danlos syndrome of severe degree were noted by Ross and Dooneief.

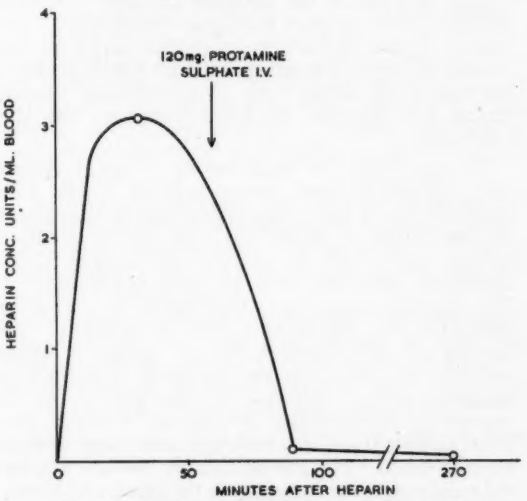

FIG. 2.—Heparin concentration in patient's blood.

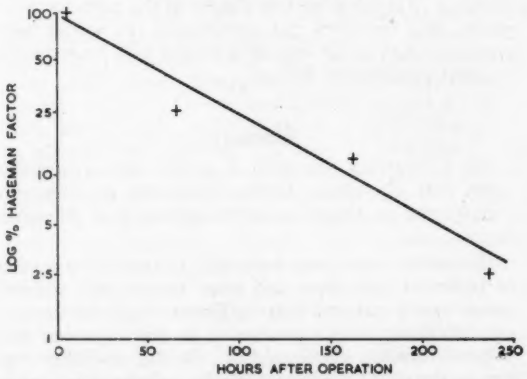

FIG. 3.—Showing disappearance of Hageman factor from the circulation.

That no technical difficulties were encountered during the operation on our patient was probably in part due to the relative mildness of his connective-tissue disorder. During 10 months since the operation no clinical evidence of breakdown in the repair of his defect or of the tissues divided during the operation has occurred.

An indicator dilution curve was recorded after the injection of indocyanin green into the superior vena cava. This showed no evidence of a significant persisting left-to-right shunt.

The excessively easy bruising experienced by patients with the Ehlers–Danlos syndrome is not a manifestation of an underlying haemorrhagic disorder. These patients, including our own, do not experience symptoms such as epistaxis, menorrhagia, prolonged bleeding from wounds, or joint haemorrhages.

Smith and Hornisher (1954) observed a prolonged blood-clotting time in a patient with Ehlers–Danlos syndrome, but no explanation is given. A detailed study of haemostasis was carried out in three patients with the Ehlers–Danlos syndrome by Frick and Krafchuk (1956), who also reviewed the earlier literature. They found no blood-clotting or platelet abnormality in their patients, but reduced capillary resistance as did some other authors. This was attributed to rupture of the vessels, which became abnormally distended owing to lack of support by the defective collagen. In other reports normal capillary resistance was recorded. The absence of overt bleeding in our patient and his relatives in spite of their easy bruising suggested that no abnormal bleeding would result from connective-tissue disorder during the operation or subsequently, as was later confirmed.

The occurrence of blood-clotting defects in patients with congenital heart disease appears to be more frequent than in other congenital disorders, as indicated by the findings of Favre-Gilly *et al.* (1951), Hartmann (1952), DeWall *et al.* (1956), van Creveld (1958), von Kaulla and Swan (1958), and Fantl and Ward (1960). It is therefore desirable to investigate the coagulation mechanism of such patients prior to operation. The clotting anomaly detected in our patient is almost certainly due to a severe congenital deficiency of Hageman factor. Patients with this anomaly do not experience haemorrhagic symptoms, although their blood-clotting times may be longer than those of many haemophiliacs. The patient and his brother, who had the same coagulation anomaly in the absence of Ehlers–Danlos syndrome, had never suffered from abnormal bleeding. Transfusion with plasma in the post-operative period was therefore not carried out, as would have been necessary in the case of a patient with haemophilia or other coagulation defects.

Summary

An 11-year-old boy with a partial atrio-ventricular canal had the Ehlers–Danlos syndrome of moderate severity and an almost complete deficiency of Hageman factor.

His cardiac defect was repaired. Despite some reports of technical difficulties and poor results with surgical procedures in patients with the Ehlers–Danlos syndrome, no difficulties were encountered in the repair of this patient's cardiac abnormality. He did not show any haemorrhagic tendency or difficulty in haemostasis prior to and after the operation.

The half-life of Hageman factor introduced by transfusion of heparinized blood was approximately two days.

Part of the investigation was supported by a grant from the National Health and Medical Research Council of Australia; one of us (R. J. S.) has been in receipt of the Sol Green Research Fellowship. Thanks are due to Dr. J. M. Gardiner and Dr. K. McLean, of the Cardiovascular Diagnostic Service of the Alfred Hospital, for their co-operation, and to Dr. P. K. Lamond, assistant pathologist at St. Vincent's Hospital, Sydney, who made available a plasma deficient in Hageman factor.

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Requirements for the protection of people employed in factories and other places to which the Factories Act, 1937, applies against ionizing radiations and other hazards arising from the use of unsealed radioactive substances are laid down in a Preliminary Draft of Regulations published by the Ministry of Labour. This draft is a complementary code to the statutory draft of Regulations, published on March 30, dealing with the protection of workers from the dangers arising from the use of "sealed sources" of radioactive substances and from machines which produce ionizing radiations. The proposed Regulations will apply to the whole range of radio-nuclides used in industry, including those used in nuclear reactors, and they will in due course replace the Luminizing Regulations, made in 1947. Unsealed radioactive substances are defined by the Regulations to include nuclear fuel elements. Maximum permissible doses, based on the recommendations of the International Committee on Radiological Protection and supported by the Medical Research Council, are laid down. Provision is made for reliance to be placed on working arrangements that provide intrinsic safety, for the instruction of workers concerned about the hazards involved, and the precautions to be taken, and also for medical supervision. Any observations on these Draft Regulations should be made in writing to the Ministry of Labour, 8 St. James's Square, London S.W.1, by July 31. (Unsealed Radioactive Substances Regulations (Draft), H.M.S.O., price 1s. 3d. net.)

LEVELS OF BLOOD-COAGULATION FACTORS DURING ANTICOAGULANT THERAPY WITH PHENINDIONE

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The complex mechanism of the factors concerned in blood coagulation has been investigated in many ways, not least among these being a study of such factors during anticoagulant therapy, and by the use of plasma from patients treated with anticoagulant drugs in cross-mixture experiments with plasma from patients having congenital coagulation defects. Earlier results from such investigations indicated a simple deficiency of prothrombin and "factor VII." It is now known, however, that Christmas factor (Douglas, 1955; Biggs, 1956; Naeye, 1957), plasma thromboplastin antecedent (Naeye, 1957), and Prower–Stuart factor (Telfer, Denson, and Wright, 1956; Hougie, Barrow, and Graham, 1957; Denson, 1958) are all reduced. Factor X* (Duckert, Flückiger, Matter, and Koller, 1955) is also reduced early in therapy. The existence of the latter factor as a separate entity, however, has not been established, and it is probably an intermediate product of thromboplastin formation.

Hörder (1958) studied levels of factor VII, Prower–Stuart factor, and prothrombin, together with the partial thromboplastin time, and thromboplastin generation in one case receiving anticoagulant therapy with the coumarin derivative phenprocoumon ("marcoumar"; 4-hydroxy-3-(1-phenylpropyl)coumarin). Hicks and Bonnin (1959) compared the reduction in plasma thromboplastic factors, the one-stage prothrombin time, and the two-stage prothrombin levels in several cases receiving anticoagulant therapy with different drugs, and concluded that the one-stage assay provided an adequate measure of the reduction in thromboplastic factors.

The present study was undertaken in order to provide a clearer insight into the fate of specific blood-coagulation factors during anticoagulant therapy with the drug phenindione ("dindevan"; 2-phenyl-1,3-indanedione), and to endeavour to discover by means of specific assays the contribution of individual factors to the overall effect of anticoagulant therapy.

Materials and Methods

Collection and Storage of Plasma and Serum Samples.—Blood was collected simultaneously into a clean sterile tube for the production of serum, and into 1/10 volume of 3.8% sodium citrate for citrated plasma. The clotted specimen was centrifuged after four to six hours and the serum separated and stored at 0° C. for periods of up to 10 days for the assay of thromboplastic factors; these assays were carried out in batches. Plasma was obtained by centrifuging the citrated blood at 2,500 r.p.m. for five minutes. Prower–Stuart factor assays and factor VII assays were performed within two to three hours of collection, and the remaining plasma was stored at 0° C. for periods of up to two weeks for the two-stage prothrombin determinations, which were carried out in batches.

Prower–Stuart Factor Assay and Specific Factor VII Assay.—These were performed as previously described (Denson, 1961).

Assay of Serum Thromboplastic Factors.—This was carried out using the thromboplastin generation method of Biggs and Douglas (1953b), with the following modifications. A chloroform extract of acetone-dehydrated human brain was used as platelet substitute (Bell and Alton, 1954). 0.1-ml. amounts of a 1/5 dilution of $Al(OH)_3$-adsorbed normal plasma, 1/10 dilution of test serum, platelet substitute, and 0.025 M $CaCl_2$ were incubated for 12 minutes, and duplicate 0.1-ml. amounts transferred with 0.1 ml. of 0.025 M $CaCl_2$ to 0.1 ml. of normal substrate plasma, and the mean of the clotting-times was recorded. The percentage of thromboplastin was obtained by reference to a calibration curve for the clotting-times of serial dilutions of thromboplastin obtained using normal serum. The pooled normal serum used for this purpose was stored for approximately the same length of time as test sera to allow for possible deterioration of thromboplastic factors.

Thromboplastic Assay of Christmas Factor.—This was determined in the same manner as the total thromboplastic factor assay, with the exception that 0.005 to 0.01 ml. of an eluate of Prower–Stuart factor obtained after electrophoresis of serum (Denson, 1961) was added to the incubation mixture in order that the result would reflect Christmas factor and not the sum of Prower–Stuart factor and Christmas factor. The amount added was determined as the amount required to produce normal thromboplastin generation using serum from the patient previously described (Prower), who is congenitally deficient in Prower–Stuart factor and whose plasma or serum contains only 7% of the latter factor.

One-stage Prothrombin Time.—This was determined, using acetone dehydrated human brain thromboplastin. Percentages were obtained by reference to a calibration curve of the clotting times of dilutions of pooled normal plasma in veronal buffer.

Two-stage Prothrombin Estimation.—This was determined by the two-stage area method of Biggs and Douglas (1953a). 10% of normal serum was added to the phenindione plasma to achieve a rate of thrombin formation comparable to that of normal plasma.

Veronal buffer (Michaelis, 1931), *p*H 7.35, was used for the dilution of all reagents. 0.025 M $CaCl_2$.

Results

Prower–Stuart factor, factor VII, prothrombin, one-stage prothrombin time, thromboplastic factors, and Christmas factor were estimated in six patients with coronary thrombosis receiving anticoagulant therapy with phenindione. The results of four of these cases are shown in Fig. 1. It was not always possible to follow these factors daily, but this was done as far as possible, at least for the first week. In order to make the figures intelligible, the one-stage prothrombin time, factor VII, and Prower–Stuart factor assays are shown in Fig. 1 (Cases I to IV(a)), and the two-stage prothrombin value, serum thromboplastic factors, and Christmas factor assays in Fig. 1 (Cases I to IV(b)). Anticoagulant therapy in all the cases followed was controlled by means of the one-stage prothrombin time with a therapeutic range of 15% to 25% (equivalent to a prothrombin ratio of 2 to 2½). Cases I to IV were given heparin in addition to phenindione at the beginning of therapy.

*Prower–Stuart factor has now been designated Factor X by international convention.

Case I illustrates the results in a patient who was maintained at the lower limits of the optimum therapeutic range with a maximum fluctuation in the one-stage prothrombin time of only ±5%. There is good correlation between the one-stage prothrombin time, Prower–Stuart factor assay, factor VII assay, and assay of total thromboplastic factors. Prothrombin shows a general downward trend, while Christmas factor levels show an immediate fall followed by a rise. The initial fall in Christmas factor values is common to the first four cases in which heparin was administered before phenindione. This fall would appear to be the result of the combined effect of heparin and phenindione, and confirms the results of Greig (1959). The rise which follows is probably due to the discontinuance of heparin and a reduction in the dosage of phenindione. There is then a further sustained fall in Christmas factor when the one-stage time is kept within the therapeutic range.

Case II, which was followed for only nine days, shows a similar correlation between the factors, and again a steep fall in Christmas factor followed by a continued rise from the fourth day of treatment which occurred three to four days before a rise in Prower–Stuart factor or total thromboplastic factors. It would again appear that this rise in Christmas factor could be attributed to the discontinuance of heparin after its combined administration with phenindione at the beginning of therapy.

Case III again shows an initial low level of Christmas factor followed by a slight rise, while the Prower–Stuart factor continued to fall. After some fluctuation, while the stabilizing dose was obtained, there is a slight but sustained rise in the value of all factors and in the one-stage prothrombin time.

Case IV was a patient who received phenindione for only five days. The Christmas factor in this case falls initially, but rises appreciably when the drug is withdrawn, while the Prower–Stuart factor continues to fall. Apart from one reduction in the two-stage prothrombin value at four days, there is virtually no alteration in the prothrombin level.

Two further cases are not shown graphically. One of these was a patient on long-term therapy who was not well stabilized during the time the factors were studied. Nevertheless, there was good correlation between the reductions of all factors. The one-stage prothrombin time was for the most part above the therapeutic range, and Christmas factor showed a negligible decrease. The second was a patient who had been maintained at a steady level within the therapeutic range for 10 days. He was given 50 mg. of vitamin K intravenously prior to major surgery. Factor VII and Christmas factor returned to normal values within 16 hours. The rise in the level of Prower–Stuart factor and prothrombin was less rapid.

In addition to the cases followed at short intervals during treatment, assays of factors were performed at

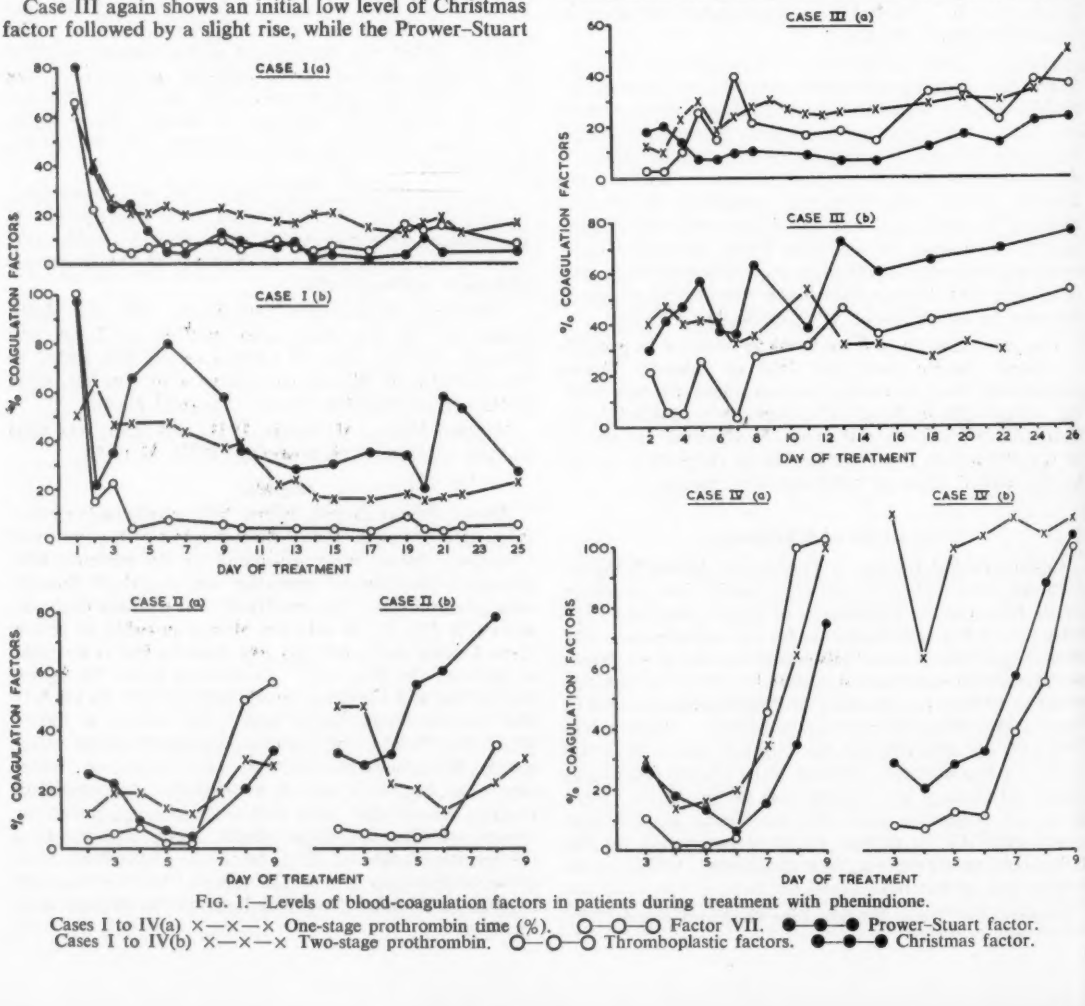

FIG. 1.—Levels of blood-coagulation factors in patients during treatment with phenindione.

Cases I to IV(a) ×—×—× One-stage prothrombin time (%). O—O—O Factor VII. ●—●—● Prower-Stuart factor.
Cases I to IV(b) ×—×—× Two-stage prothrombin. O—O—O Thromboplastic factors. ●—●—● Christmas factor.

random times in a further group of patients on long-term and short-term therapy. The results are presented in the Table.

Values of Blood-coagulation Factors at Random Times During Long-term and Short-term Phenindione Therapy

Case	One-stage Pro-thrombin Time %	Prower–Stuart Factor %	Factor VII %	Two-stage Pro-thrombin %	Serum Thrombo-plastic Factors %	Christmas Factor %
1	46	32	27	70	44	100
2	35	19	21	—	15	100
3	34	46	46	80	85	100
4	15	4	3	12	25	79
5	22	9	10	14	42	90
6	33	30	14	40	75	88
7	30	6	9	45	62	85
8	17	12	9	18	17	54
9	18	17	2	23	23	37
10	20	17	10	19	10	28
11	15	19	1	19	12	28
12	17	12	11	50	25	67
13	11	2·5	22	38	14	49
14	37	18	43	40	80	95
15*	7	10	0·5	43	15	37
16*	28	36	32	92	51	63
17*	13	7	6	49	9	35
18*	25	10	2	—	35	77
19*	18	5	16	17	3	57

* Short-term cases.
Long-term cases had received therapy for two to five years and short-term cases for two to four weeks.

Reduction in Factor VII During Therapy

In all the cases studied correlation of the various factors with the one-stage prothrombin time was extremely good. Factor VII is the most sensitive in its response to changes in dosage of phenindione. There is a precipitous fall early in treatment, and an equally steep rise when the drug is withdrawn or the dosage is reduced. Minor alterations in dosage produce similar fluctuations in factor VII content which precede changes in other factors. An example is Case III on the third to fifth day of treatment, when factor VII rises as a result of a reduction in the dose of the drug, while the Prower–Stuart factor is still affected by the drug and continues to fall as a result of previous dosage. A similar example is Case IV on the fifth to seventh day of treatment, and other examples may be noted.

Reduction in Christmas Factor During Therapy

Christmas factor appears to show a sharp fall early in therapy and then follows very closely the values for Prower–Stuart factor and total serum thromboplastic factors, but at a higher level. The lowest value obtained for Christmas factor was 21%, although the one-stage prothrombin time was below the minimum of the therapeutic range on many occasions. This agrees well with the results obtained by Naeye (1957), who showed values for Christmas factor of 25 to 70% corresponding to values of 10 to 35% for "stable factor." It would thus appear that Christmas factor is not grossly depressed when the one-stage prothrombin time is maintained within the therapeutic range. This is illustrated in Fig. 2, where Christmas factor levels are compared with corresponding one-stage prothrombin-time values. As can be seen from the Table, levels of Christmas factor encountered during long-term therapy agree as a whole with values obtained during short-term therapy. In those cases with one-stage times above the therapeutic range the Christmas factor values are almost normal, the lowest value being 63%.

The low values of Christmas factor encountered early in therapy after the administration of heparin are in accordance with the results of Greig (1959), and substantiate the earlier observations of Walker and Hunter (1954) and Verstraete and Vandenbroucke (1956), who showed that in some cases early in anticoagulant therapy thromboplastin generation was impaired while the one-stage time showed little or no change.

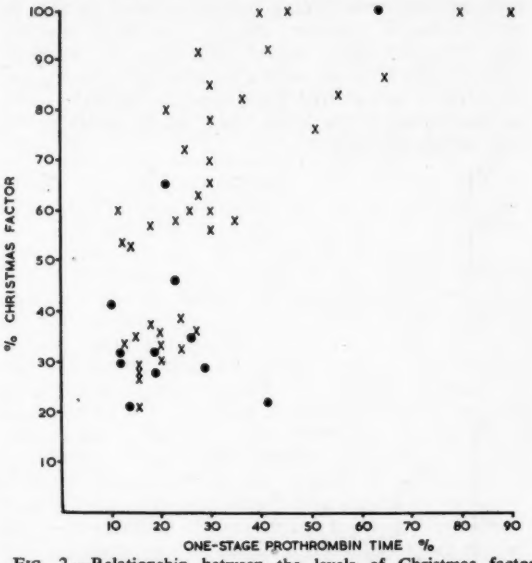

FIG. 2.—Relationship between the levels of Christmas factor corresponding to one-stage prothrombin times in patients receiving phenindione therapy. Levels obtained within the first four days are represented by dots, and the remaining values by crosses.

Reduction in Prothrombin During Therapy

Prothrombin concentration, as measured by the two-stage technique, is relatively insensitive to changes in dosage of phenindione. There is little reduction when the one-stage prothrombin-time value is above the therapeutic range or when the drug has been administered for only a few days (Case IV). If the one-stage time is maintained within the therapeutic range, prothrombin values show a gradual downward trend, until after one to two weeks a stable value of 10 to 30% is obtained. Short-term cases after one to two weeks' therapy show values similar to those of cases on long-term therapy, as can be seen from the Table. For cases having one-stage prothrombin-time values above the therapeutic range, corresponding prothrombin values are between 40 and 92%, while cases showing one-stage prothrombin-time values in or below the therapeutic range have corresponding prothrombin values ranging from 12 to 50%.

Reduction in Prower–Stuart Factor During Therapy

Prower–Stuart factor is reduced after four to seven days of therapy to stable values of about 3 to 15%, similar to values for factor VII, when the one-stage prothrombin time is maintained at a steady therapeutic level. The relationship between Prower–Stuart factor and the one-stage prothrombin time is shown in Fig. 3, where high values of Prower–Stuart factor corresponding to one-stage times within the therapeutic range are clearly distinguished as those occurring within the first four days of therapy.

Phenindione thus elicits a much slower response in Prower–Stuart factor than in factor VII, possibly by virtue of the longer survival time *in vivo* of Prower–Stuart factor. Reduction of this thromboplastic factor

may be the most important consideration in haemorrhagic episodes, and, since it is liable to less rapid fluctuation than factor VII, its parallel estimation may be of value in the control of therapy.

Unfortunately, it has not been possible to obtain sufficient cases manifesting haemorrhage to be able to make a useful analysis. Plasma and serum samples were obtained from several such cases at intervals varying from 12 to 36 hours after bleeding episodes, but the level of factors after these intervals probably bears no relationship to the levels which would obtain at the time of haemorrhage.

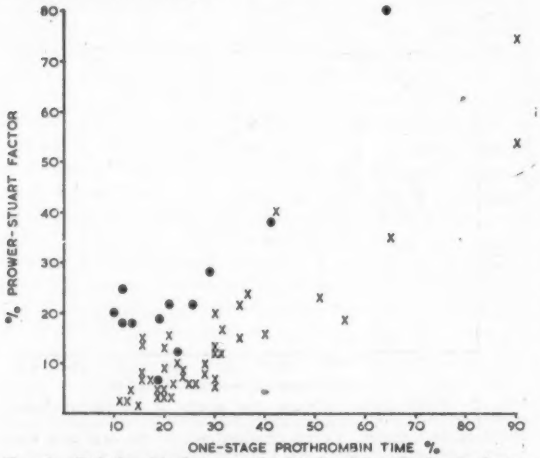

FIG. 3.—Relationship between the levels of Prower–Stuart factor corresponding to one-stage prothrombin times in patients receiving phenindione therapy. Levels obtained within the first four days of treatment are represented by dots and the remaining values by crosses.

Assay of Serum Thromboplastic Factors

The values for this assay agree closely with the values of the sum of Christmas factor and Prower–Stuart factor in some cases; in others there is complete lack of agreement. The explanation for this might be found in the existence of yet another serum factor. This anomaly, however, might be accounted for by the fact that the thromboplastic assays of both Prower–Stuart factor and Christmas factor are less sensitive than the corresponding one-stage assay methods.

Thrombotest Values in Parallel with Specific Assays

The thrombotest value, one-stage prothrombin time, Prower–Stuart factor, factor VII, and Christmas factor were estimated in two patients receiving anticoagulant therapy with phenindione and heparin. The results are shown in Fig. 4 (Cases VII and VIII).

Christmas factor again shows a low level after the first two days during the coincidental administration of heparin and phenindione. The thrombotest value closely follows the one-stage prothrombin time, but at a lower level. The relative insensitivity of the thrombotest reagent to Christmas factor is clearly demonstrated. High thrombotest values coincide with low Christmas factor values at one or two days, and after five to eight days' therapy the thrombotest values rise slightly in parallel with the one-stage values, while the Christmas factor continues to fall.

Discussion

It is extremely difficult to interpret the levels of the various coagulation factors during phenindione therapy when the one-stage prothrombin time is fluctuating. Factor VII may rise as much as 50% within 24 hours of discontinuing the drug, while thromboplastic factors may still be falling or be at extremely low levels. Conversely, if a patient is maintained at a level above the therapeutic range and dosage is increased, factor VII may drop precipitously while thromboplastic factors are still at a level conducive to thrombosis. It is this extreme sensitivity of factor VII to varying dosage and its effect on the one-stage time which renders interpretation and the control of therapy difficult. In this connexion it is essential to obtain blood samples during thrombotic or haemorrhagic episodes if any attempt is to be made to correlate the levels of specific factors with thrombosis or haemorrhage, and even under these circumstances values obtained must be related to the previous day-to-day trends.

With the exception of a small minority of resistant cases, there is a general reduction of all factors in response to phenindione therapy, and while it is not suggested that this reduction is the same qualitatively and quantitatively from patient to patient, nevertheless a general pattern is followed. One clear-cut fact emerges: it is almost certain that when stabilization is obtained within the therapeutic range, prothrombin, for example, will not be greatly reduced, while factor VII and Prower–Stuart factor are at high levels; so, too, Christmas factor will not be so low as to predispose to haemorrhage, while prothrombin and the remaining factors are not significantly reduced. The effect of phenindione is to depress these factors at what would appear to be a common locus, and the rate at which a factor disappears or reappears is probably governed by its survival time and rate of production in the liver.

Intravascular clotting is primarily due to vascular defects, and it is held that the intrinsic thromboplastin system is probably of more importance in this respect than the activation of tissue thromboplastin by factor VII. In view of this, the control of therapy by a method well suited to reveal deficiencies of factor VII is perhaps undesirable. Loeliger, Esch, Haar, Romeny-Wachter, and Booij (1960), however, have provided evidence to show the importance of factor VII in the rapid activa-

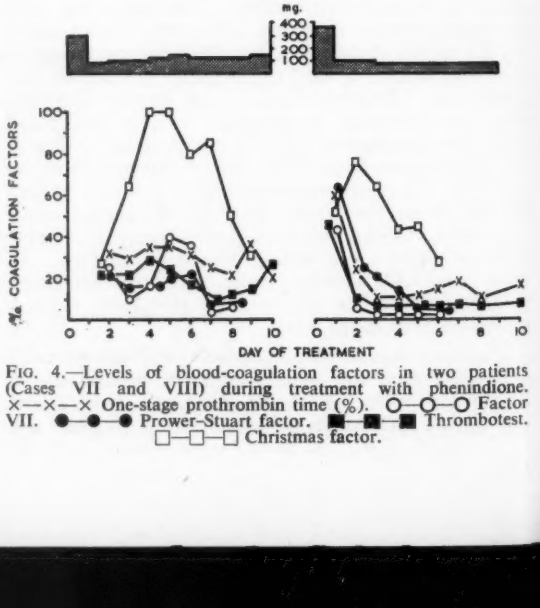

FIG. 4.—Levels of blood-coagulation factors in two patients (Cases VII and VIII) during treatment with phenindione. ×—×—× One-stage prothrombin time (%). ○—○—○ Factor VII. ●—●—● Prower–Stuart factor. ■—■—■ Thrombotest. □—□—□ Christmas factor.

tion of extrinsic thromboplastin derived from damaged endothelium, resulting in the formation of a mural thrombus. The latter in turn activates the intrinsic thromboplastin system, resulting in a slowly growing thrombus. If this postulate proves to be correct then the one-stage prothrombin time, because of its sensitivity to changes in factor VII concentration, is well suited to the control of anticoagulant therapy. The test, however, is not intended as a technique of scientific accuracy, and frequently more harm than good is done by the over-enthusiastic adjustment of dosage as a result of smaller day-to-day differences in values which are often not outside the limits of technical errors, and which are largely due to the sensitivity of the method for factor VII. The method does, however, reflect the summated deficiencies of factor VII, prothrombin, and Prower–Stuart factor, and in this respect is probably a better guide to normal haemostasis or impending haemorrhage than assay of one isolated factor.

In a search for the panacea many modifications and ancillary methods have been tried. The one most extensively used has been the "prothrombin and proconvertin" method of Owren and Aas (1951). Toohey (1958), Allington (1958), and Biggs and Macfarlane (1957) have reported favourably on the use of this method in the control of anticoagulant therapy. Toohey (1958) reserves this method for short-term in-patient treatment because of its greater sensitivity, and prefers the Quick one-stage time for long-term out-patient treatment. In the latter connexion it may be that the greater stability obtained when using the Quick one-stage method is due to the less frequent change in dosage in response to minor variations in the one-stage time, these variations remaining undetected during long-term therapy. Undoubtedly the "prothrombin and proconvertin" method reflects changes more quickly than the Quick one-stage prothrombin time, which suggests that the former method is more sensitive to changes in factor VII concentration.

Sise, Lavelle, Adamis, and Becker (1958) have suggested the simultaneous determination of prothrombin and the Quick one-stage prothrombin time as a means of controlling therapy. This method is suggested because of the closer association between prothrombin and thrombotic or bleeding episodes. Again, the importance must be stressed of obtaining true values at the time of thrombotic or bleeding episodes, since any delay in obtaining specimens may result in rapid fluctuations of factor VII.

Bachmann, Duckert, and Koller (1958) have tentatively suggested simultaneous determinations of Prower–Stuart factor and the Quick one-stage prothrombin time, with reduction of dosage when the former value is below 12%, regardless of the one-stage prothrombin time. This may prove to be a useful adjunct in cases which are difficult to stabilize.

It is doubtful whether methods which attempt to estimate more and more factors will give better control of therapy. The thrombotest of Owren (1959) has a reduced sensitivity to the prothrombin complex factors, but estimates Christmas factor in addition. If it can be shown that Christmas factor is reduced to haemorrhagic levels in a reasonable proportion of cases while other factors are at high levels, then a good case exists for a method which will include the assay of Christmas factor even at the expense of less sensitivity for the other factors. In the present study, levels of Christmas factor followed very closely levels of Prower–Stuart factor, and were never depressed disproportionately except within the first few days of therapy. A method which detects the initial low values of Christmas factor after heparin administration will demand a reduction in dosage, and consequent upon this there will be a sharp rise in factor VII. If, then, one accepts the postulate that factor VII is the most important factor in initial mural thrombus formation, then such reduction in dosage will increase the risk of recurrent thrombosis. The thrombotest method, however, may well give safer control of therapy than existing methods, although in routine practice the complexity of the reagent is a disadvantage if this has to be made and standardized in the laboratory concerned. The use of an expensive commercial reagent of only broadly specified composition is equally undesirable, although the simplicity of technique no doubt compensates for this. Evidence will be presented in a further publication to demonstrate the almost complete insensitivity of the reagent to Christmas-factor deficiencies and the infinitely greater sensitivity which is shown to both factor VII and Stuart–Prower factor, although both the latter factors are uninfluenced by the addition of cephalin to the reagent. It certainly cannot be described as a "test which is equally sensitive to both coagulation systems." The sensitivity to Christmas factor may appear at first sight to be at least a comfort to those responsible for the control of anticoagulant therapy. Such reliance upon a false sensitivity, however, may be misleading or even hazardous when it is realized that a plasma sample having a Christmas assay of less than 1% may show a value of between 50% and 80% by the thrombotest method.

The effect of variable rates of absorption of oral anticoagulants and the added effect of diet on this, the variable vitamin K intake, the potentiating effect of antibiotics and drugs, and secondary infection will affect equally all methods used to control therapy.

The extremely benign effects of phenindione, in comparison with the erratic response elicited by the earlier coumarin-type drugs, is unquestionable. This is reflected in the fact that it has been extremely difficult to obtain cases showing haemorrhagic episodes during phenindione therapy.

In conclusion, it is true that specific and more involved methods may be appropriate to the specialized anticoagulant laboratories, and may lead to better control of therapy as a result of careful and exacting technique. For the busy clinical laboratory, however, simplicity of technique compatible with reasonable accuracy is of paramount importance.

Summary

The levels of factor VII, Prower–Stuart factor, Christmas factor, total thromboplastic factors, and prothrombin have been studied at intervals in patients receiving anticoagulant therapy with phenindione.

The reduction in the concentration of these factors correlates well with the values for the one-stage prothrombin time when stable values for the latter are obtained.

Factor VII rises and falls precipitously in response to changes in dosage, and while the decrease in factor VII is the earliest indication of a decrease in other factors, the equally rapid increases often mask the continued reduction in the concentration of other factors.

Christmas factor is reduced early in therapy, probably as a result of high dosage of phenindione in association with the administration of heparin.

The thrombotest method is relatively insensitive to a reduction in Christmas factor, but correlates well with the one-stage prothrombin time.

For the routine clinical laboratory the one-stage prothrombin time as a means of controlling therapy is perhaps still the method of choice, by virtue of its technical simplicity.

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MULTIPLE PAINLESS GLOMUS TUMOURS

BY

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While still regarding the whole range of glomus-celled anomalies as variants on the same theme, it seems both reasonable and practical to delineate certain clinical types which correspond to recognizable variants in the histological structure, and require quite different treatment.

It is becoming clear that two forms of glomus anomaly occur, neither being a true neoplasm. The first is the solitary painful lump which is an organoid malformation or hamartoma, the other being the diffusely distributed multiple painless lesions which are more telangiectatic in nature.

Two cases showing a familial relationship are reported here to indicate the differences in this second group from the typical painful glomus tumour.

Case 1

A woman aged 24 sought medical advice because of the progressive enlargement of a lesion on the dorsum of the right hand. This lesion had appeared six or seven years previously as a soft, slightly raised lump beneath the skin, but in the past two years had become bluish in colour, and had doubled its size in the past six months. Several dilated veins adjacent to the lesion had been present for a few months, and her main concern was the unsightly appearance of the lump; she also had a mild curiosity regarding its nature. At no time had it been painful or tender.

Examination revealed, in the centre of the dorsum of the right hand, a bluish dome-shaped mass, 1.5 cm. in diameter, soft in texture, compressible without complete obliteration, non-pulsatile, and of the same temperature as the surrounding skin to rough clinical tests. Three distended veins passed distally and one proximally from the lesion. A separate small mass 3 mm. in diameter, with similar features, was present just under the skin, about 3 cm. proximal to the main mass. The lesion was thought to be an unusual variety of arteriovenous communication, and local excision was advised.

At operation the dermis was closely adherent to the surface of the central vascular mass, which consisted of three or four large tortuous cavernous masses from which several veins radiated both up and down the dorsum of the hand and obviously having the highest point of venous pressure at the mass rather than distally at the fingers. Only one small artery entered the mass on its deep aspect.

Histologically the mass consisted of several groups of large blood spaces surrounded by collars of fairly regular small glomus-type cells, which were sometimes several layers deep but often only one or two cells deep (Figs. 1 and 2). In some of the cellular areas a mucoid material was present between the cells. The lobulated blood spaces were well separated from the surrounding fat.

On further questioning the patient stated that several small bluish spots in the skin of her arms, legs, and breasts had begun to appear after the age of 8 years. The spots

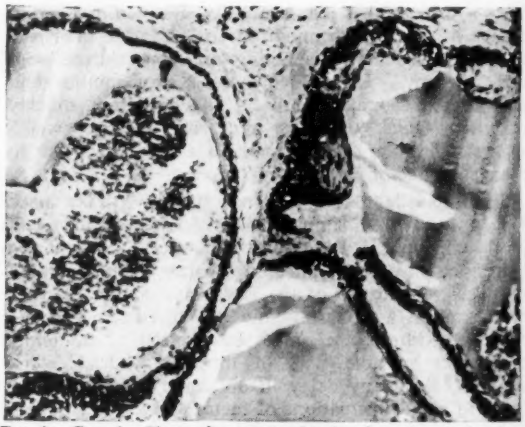

FIG. 1.—Case 1. Photomicrograph of lesion from hand, showing large vascular spaces lined by glomus-type cells. (×122.)

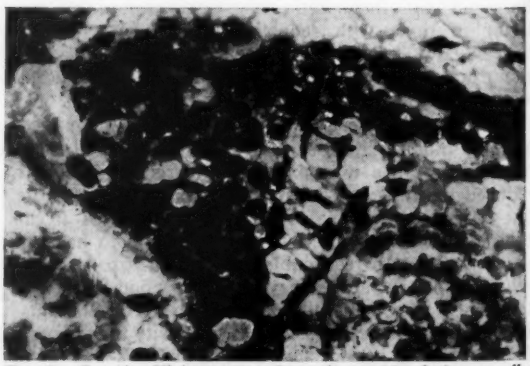

FIG. 2.—Case 1. Higher-power photomicrograph of glomus cells in trabeculae of lesion. (×540.)

have appeared roughly in episodes, when four or five may have become visible over a few months but nothing more for some years. Beginning as tiny pin-point spots, these slowly enlarged, and, on becoming 3 to 4 mm. in diameter, took on a low dome-shaped contour. Most of these lesions were single, but several appeared as small clusters; one in particular she related to the site of a Mantoux injection on the right forearm.

There has never been any spontaneous or induced pain in these lesions or any symptoms produced by change in the surrounding temperature.

Case 2

This patient, a man aged 26, is the only brother of the previous patient. In the same position, on the dorsum of his right hand, there is a raised bluish lump 1 cm. in diameter and identical clinically with the lesion removed from the same area on his sister's right hand (Fig. 3). This lesion had been noticed for over 10 years, and there was a history of the skin in this region having been punctured by a nail at football many years before, but no scar could be detected.

On the right upper arm there was a cluster of several blue spots ranging from 1 to 3 mm. in diameter, and related by the patient to his vaccinations in this area some years previously, but no scar was visible at this site (Fig. 4). On both arms and both legs, and on the back of the trunk and buttocks, many similar lesions were present. These ranged from tiny impalpable but completely collapsible areas clearly composed of large blood lakes to raised palpable masses irregular in outline and only partly compressible. Two such bluish clusters of tissue which had been present on the back of the left thigh for five years were regarded by the patient as "just varicose veins." There had been no pain, tenderness, or temperature changes associated with any of the lesions.

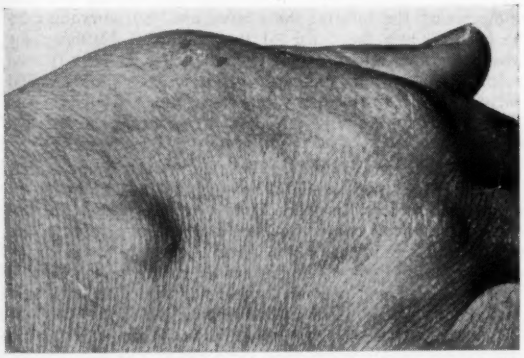

FIG. 3.—Case 2, brother of Case 1. Raised bluish compressible lump on dorsum of right hand clinically identical with lesion excised from his sister.

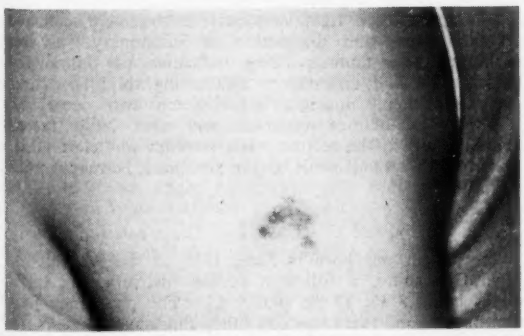

FIG. 4.—Case 2. Cluster of typical lesions on outer aspect of right arm.

It was impossible to count the total number of lesions present on either of these patients because the range passed smoothly from large to barely visible, and presumably to the microscopic which may later become visible.

Both brother and sister are emphatic that their late father had, for as long as they could remember, a raised bluish lump on the dorsum of the right hand similar to their own, although smaller in diameter.

Discussion

Since the classical paper of Masson (1924) first related the extremely painful subcutaneous nodules, which had been described by Cheselden as long ago as 1740, to the neuro-myo-arterial glomus apparatus, several hundred such tumours have been reported. It is possible to divide these reports into three clinical groups.

1. Solitary glomus tumour: this being the commonest presentation with a very painful nodule, usually on an extremity, associated with radiating pain triggered by touch or temperature change, sometimes with demonstrable changes in the skin circulation of the whole limb and completely cured by surgical extirpation.

2. Multiple painful glomus tumours: rarely more than three or four in number, but each presenting the same features as a solitary glomus tumour. As Rowntree (1952) has indicated, these are always well localized to a circumscribed area of the body. In such a local grouping the tumours may also occur in deeper tissues such as beneath the deep fascia (Rowntree, 1952) or within a bone (Bergstrand, 1937). Both clinically and histologically these tumours are identical with the solitary glomus tumour, and seem merely to represent a regional tendency to the formation of this lesion.

3. Multiple painless glomus tumours: in which the lesions are numbered in dozens, are widely distributed, and give rise to no symptoms (Weidman and Wise, 1937). Both clinically and histologically these lesions appear to be primarily vascular in origin, and at the other end of the scale from the much more cellular, very painful glomus nodules. While it is realized that exceptions do occur, it is felt that such a generalization is both warranted and useful. A case such as that of Eyster and Montgomery (1950), in which two painful lesions were present as well as several dozen painless lesions, probably represents, as those writers suggest, a transitional form between the two extremes of structure.

It is now generally accepted that the nature of the solitary glomus tumour is that of an organoid malformation or hamartoma, in which the masses of glomus cells and nerve endings aggregated about the vascular spaces roughly simulate the structure of the normal glomus. Three histological gradings are recognizable, depending on the relative proportions of glomus-cell proliferation to the size of the vascular lumina. Thus we find lesions with normal proportions, others with relatively more cellular structure, and finally those predominantly vascular in structure. No definite correlation has been attempted between the severity of symptoms and the histological structure. Slepyan (1944) compared the histology of a painful glomus tumour with that of a painless glomus tumour from the same patient, and indicated that the lesion giving rise to symptoms was the more cellular. In a series such as that reported by King (1954) it is of interest not only that the multiple lesions were all vascular but that several of the vascular lesions were painless, whereas all the cellular lesions were painful.

The present cases indicate that, since the multiple painless lesions are of the vascular type, this correlation is probably significant. However, there is no explanation why a solitary cellular painful malformation should occur in one person while multiple vascular painless lesions appear in another. It is probable that two quite different factors are operating to produce these two groups of cases. The solitary cellular lesion represents an isolated malformation occurring sporadically and quite accidental in origin. The multiple vascular telangiectatic type of anomaly may be genetic in nature as suggested in this instance, where brother and sister are similarly affected; and they described an identical lesion on their late father. The diffuseness of the distribution of these telangiectatic lesions favours the probability of such a general somatic factor being responsible. The progressive appearance over several years is still consistent with our knowledge of glomus-cell production, this being normally a post-natal development, and may in fact occur anywhere from aggregation and hyperplasia of local spindle cells normally in and around any blood-vessel walls. The possible initiation of some lesions by local trauma is suggested in the history of both cases reported, and it may be significant that each injury involved a puncture wound, by needles and once by a nail.

Thus it seems that the basic abnormality in these patients is vascular, the occurrence of telangiectases being distinguished by a hyperplasia of glomus-type cells irregularly scattered in the walls. It is suggested that such multiple painless lesions can be separated from the solitary lesion, wherein cellular proliferation is more prominent, and that nearer-to-normal glomus structure is reproduced both structurally and functionally.

Summary

Glomus-cell development is a normal postnatal event, and abnormalities of this process may result in a range of lesions showing different degrees of glomus-cell hyperplasia and different proportions of vascular to cellular components in these lesions.

While the usually solitary cellular painful glomus "tumour" or hamartoma is well recognized, the multiple, more vascular or telangiectatic type of painless lesions is not.

Two cases, those of a brother and sister, are reported with multiple painless glomus lesions, and the significance of these lesions is discussed in relation to the present concepts of glomus-cell abnormalities.

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A booklet, *Notes on W.V.S. Health and Hospital Work*, gives a bird's-eye view of the work done by the Women's Voluntary Services in hospitals (canteen work, shopping, library services, work in out-patient departments, and staffing telephone trolleys), in the blood transfusion, mass radiography, and hospital car services, and in their work for sick and handicapped people in the community. There is a list of useful books and an index. Inquiries should be sent to W.V.S. Headquarters, 41 Tothill Street, London S.W.1.

SYNDROME OF COLOBOMA WITH MULTIPLE CONGENITAL ABNORMALITIES IN INFANCY

BY

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During the past ten years coloboma of the eyes has been noted in four infants in our paediatric wards, and in every case it has been accompanied by other congenital abnormalities, particularly affecting the brain and heart. The main features of these cases are here described.

Case 1

A male infant was admitted to the Warrington General Hospital when 12 days old, with a history of increasing jaundice since birth, slowness in taking feeds, and general weakness. He had been born at home, a forceps delivery complicated by intrapartum haemorrhage. The birth weight was 7 lb. 8 oz. (3,400 g.). The mother's pregnancy was normal. There are two other children, both normal.

On admission he was jaundiced and a large cystic mass could be palpated, filling the lower part of the abdomen. Bilateral colobomata in the "typical" position were noted, involving the choroid, retina, and iris of both eyes. A systolic murmur could be heard to the left of the sternum. He had to be tube-fed. He was transferred to the neonatal surgical unit at Alder Hey Children's Hospital, where an intravenous pyelogram showed a normal right kidney but no excretion of dye on the left side. Laparotomy revealed the presence of an enormous hydronephrosis on the left side, compressing the inferior vena cava and the common bile-duct, this being the cause of the jaundice. Nephrectomy was performed and the jaundice gradually faded. It soon became evident that he had a severe degree of cerebral palsy. Head control and sitting were much delayed; both arms were spastic and his legs were small, weak, and hypotonic.

At the time of writing, aged 5 years, he could not assume the sitting position unaided, nor could he maintain his weight on his legs for more than a few seconds. He was speechless and his comprehension was almost negligible. He was able to see objects which were close to him, but vision was poor and there were constant searching movements of his eyes. He could pick up large objects but dropped them immediately. His head circumference was only 18¼ in. (47.5 cm.). The cerebrospinal fluid was normal. Cardiac enlargement was present with cyanosis of the lips, fingers, and toes. There was a systolic thrill and murmur, maximal in the second left intercostal space. The E.C.G. showed right ventricular dominance and *x*-ray examination and cardioscopy showed right ventricular enlargement, concave pulmonary arc, and diminution of pulmonary vascular markings, these findings being indicative of pulmonary stenosis. He had difficulty in swallowing solid food and severe nutritional anaemia occurred on two occasions. Respiratory infections occurred and also large faecal accumulations in the rectum. His scrotum was cleft—this, together with a small penis, giving an almost hermaphrodite appearance.

Case 2

This patient was born in June, 1955, at the Warrington General Hospital, a full-term normal delivery, his birth weight being 8 lb. 15 oz. (4,055 g.). The pregnancy had been normal and there was one other child, aged 3 years, in good health. A number of congenital abnormalities were noted after birth, including talipes equinovarus of the left

foot and right inguinal hernia. There was a small fatty pad over the lower lumbar region of the spine, and radiographs of the spine showed a hemivertebra at the lumbosacral junction. "Typical" colobomata of both eyes involved the choroid, retina, and iris. Searching nystagmoid movements of the eyes denoted defective vision. His urine was normal on laboratory examination and his blood urea was 64 mg./100 ml. In view of the renal abnormality found in the previous case an intravenous pyelogram was done, but this was normal.

His head began to enlarge rapidly. His head circumference at birth was 14 in. (35.5 cm.), by the age of 3 weeks it was 15½ in. (29.4 cm.), and at 2 months had reached 16½ in. (42 cm.). Lumbar air encephalography showed a large amount of subarachnoid air and some dilatation of the ventricles. Feeding was always difficult. The legs became spastic, particularly on the right side, and there were bilateral extensor spasms. His arms were spastic and his hands remained clenched. He could hold objects but made no attempt to grasp. At the age of 1 year he was unable to sit up and comprehension seemed almost absent.

Soon after birth a loud systolic murmur could be heard to the left of the sternum. His heart enlarged, he was dyspnoeic at rest, and there was marked lower-rib recession. The apex beat extended out to the anterior axillary line and there was heaving of the right ventricular outflow tract. The pulmonary second sound was accentuated and split. A loud systolic murmur was heard, maximal at the end of the third left intercostal space, and there was a low-pitched diastolic murmur at the apex. *X*-ray examination and cardioscopy showed an enlarged pulmonary arc with left ventricular enlargement and increased hilar and pulmonary vascularity. In the E.C.G. there was an R wave with an upright T wave, suggesting left ventricular diastolic overload. These findings pointed to a diagnosis of persistent ductus arteriosus. He suffered from recurrent respiratory infections and died from pneumonia in October, 1956.

Case 3

This infant was born in November, 1959, at a Warrington maternity home, a normal delivery, her birth weight being 4 lb. 10 oz. (2,100 g.). Her mother had had a lobectomy in 1950 for bronchiectasis, but the pregnancy was uneventful. The infant had an abnormal facial appearance with wide-set prominent eyes, strabismus, and some beaking of the nose, superficially resembling Crouzon's disease. A small cleft was present in the posterior part of the soft palate. Coloboma was present in the left eye in the line of the foetal fissure, affecting the iris and the marginal part of the lens in the 7 o'clock meridian. There was some thinning of the choroid and retina, possibly representing a minimal degree of coloboma.

A loud systolic murmur could be heard to the left of the sternum, and subsequent cardiac investigation revealed the following signs: no dyspnoea or cyanosis at rest; slight upper sternal prominence; weak pulmonary second sound; and grade 4 high-pitched systolic murmur without a thrill, maximal in the second left interspace. A phonocardiogram showed an ejection-type systolic murmur with variable splitting of the pulmonary second sound and low amplitude of the second element. *X*-ray examination showed moderate cardiac enlargement involving the right ventricle, with full pulmonary arc and pulmonary oligaemia. A diagnosis of pulmonary stenosis was later confirmed by cardiac catheterization. Cyanosis and clubbing of the fingers have since developed.

The infant has failed to grow, her weight at the age of 9 months being only 8 lb. 9 oz. (3,885 g.). A radiograph of her wrist does not yet show any carpal centres. She is unable to sit up or even hold her head erect when lifted up. Her legs tend to remain in the foetal position and a persistent grasp reflex is present in the hands and feet. The knee- and ankle-jerks in the right leg are exaggerated and her right hand tends to remain clenched. She cannot hold objects in her hands and she does not observe her surroundings with much sign of comprehension. The head circumference is only 15½ in. (39.4 cm.), the *x*-ray picture of the skull being normal. There has obviously been a serious failure of brain development. The infant's urine was shown to be normal apart from a slight trace of albumin, and a hyalase pyelogram did not reveal any developmental abnormality of the kidneys.

Case 4

This patient was born at home in July, 1960. During labour some bleeding occurred per vaginam, which prompted the midwife to make a vaginal examination. A soft mass was palpable, associated with some further bleeding, and it was thought to be a placenta praevia. In actual fact a large meningo-encephalocele was presenting, and it had partially ruptured. The mother, who used to suffer from epilepsy, had not been ill during the pregnancy, although she had fallen downstairs at the fifth week without injuring herself. There is one other child aged 4 years, and she is quite healthy. The birth weight was 6 lb. (2,720 g.).

The infant was admitted to the Warrington General Hospital a few hours after birth. His head looked small, and projecting from a midline hiatus in the region of the posterior fontanelle was a large red mass of cerebral meninges which also contained some brain tissue. The encephalocele seemed acutely tender and if lightly touched made the infant cry. The other major abnormality was bilateral colobomata in the line of the foetal cleft, involving the choroid, retina, and iris of each eye. Surprisingly enough, the infant thrived, taking feeds hungrily, his colour was good, and the limb tone was normal without evidence of weakness. He was transferred to the neonatal surgical unit at Alder Hey Children's Hospital. The sac, which had become infected, was excised together with some infected brain tissue, the meninges were sutured, and the skin was sutured over the deficiency in the skull.

The infant at the time of writing was 11 weeks old and had continued to make good progress. The head looked a little dolichocephalic due to the bulging of the scalp over the occipital foramen. There was ability to see, as he seemed to take notice of his surroundings. He held his head erect and made some attempt to hold objects placed in his hands. In this case there was no evidence of cardiac or renal disease.

Discussion

The eyes of all four children were affected by "typical" colobomata, this term implying that the coloboma occurs in the line of the foetal fissure. In three of the cases the colobomata were bilateral, involving the choroid, retina, and iris, the remaining case having a unilateral coloboma of the iris and lens with minimal changes in the retina and choroid. The most widely held theory of causation of coloboma of the choroid is that it is due to an ectodermal epiblastic hyperplasia of the lips of the foetal fissure, with excessive growth of the inner retinal layer leading to its eversion. If there is a coincident coloboma of the iris the aetiology is identical, as there is then a deficiency of the rim of the optic cup in the line of the foetal cleft (Mann, 1937).

Each of the children described has suffered a serious error of brain development, and three of them also have grave congenital heart disease. It is interesting to note that pulmonary stenosis was present in two of the three cardiac cases. The other major abnormality occurring in one of the children was congenital hydronephrosis. None of these congenital abnormalities are particularly

uncommon *per se*, but it is apparent that children with typical colobomata of the choroid, retina, and iris are liable to have multiple congenital abnormalities, particularly affecting the brain and heart.

The aetiology of congenital developmental anomalies still remains obscure. In none of these families was there any history of hereditary or familial incidence of coloboma or any other congenital abnormality. A genetic theory of causation therefore is not likely but certainly cannot be ruled out. Various infections of the mother during pregnancy may cause developmental errors. It is well known that rubella infection during the early months of pregnancy can cause cataract, congenital heart disease, deafness, and mental retardation. In none of these cases was there any history of infection, although a virus infection during pregnancy could pass unnoticed. There is a widely held theory that the same agent can produce different types of deformity, depending on the stage of development of the embryo during which it acts. Its action is most marked on structures which are actively differentiating. Soon after gastrulation the neural tube, optic vesicle, and the heart are in an active state of differentiation, all at the same time, and are all at the anterior apical end of the embryo. It might be expected, therefore, that an adverse environment between the first and second months of pregnancy could produce coincident damage to the eye, brain, and heart. Even at this stage the metanephric duct and palatine shelves are present but possibly not actively differentiating, as congenital hydronephrosis and cleft-palate were not a constant feature in all the cases.

There are not many references in recent literature to similar cases, but Rolando and Jemma (1959) have recorded one such case of a girl aged 7 years with bilateral "typical" colobomata of the choroid, retina, and iris, who had congenital heart disease due to a patent interventricular septum; also a congenital kidney defect with a double renal pelvis and ureter on one side and a pelvic kidney with short ureter on the other. The child's mother had contracted virus hepatitis early in pregnancy, and it was thought that this might have been the causative agent. It is possible that detailed investigation of cases similar to those described might prove of value in establishing the aetiology of congenital developmental abnormalities in the human embryo. Preliminary investigations point to some chromosome abnormality in Case 1.

Summary

A syndrome is described of congenital colobomata associated with other congenital developmental errors, particularly of the brain and heart.

Details are given of four cases, with some discussion of aetiology.

I thank Professor John D. Hay and Dr. Olive Scott for cardiac investigations at the congenital heart department of the Royal Liverpool Children's Hospital; Mr. P. P. Rickham and Mr. J. H. Johnston for surgical investigation and treatment at the neonatal surgical unit at Alder Hey Children's Hospital; and Mr. A. V. Clemmey for ophthalmic investigations and reports.

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Medical Memoranda

Polycythaemia and Renal Carcinoma

In recent years the coexistence of polycythaemia with renal carcinoma has been reported in a number of cases, and it seems likely that some 4% of patients with renal carcinoma may show polycythaemia. The majority have been recognized in retrospect, although the polycythaemia may be the presenting symptom. Although the mechanism is not established, overaction of erythropoietic principle may be considered.

CASE REPORT

A woman of 73 living in the Yorkshire Wolds had for a year complained of redness of the face and headache. In May, 1958, painless haematuria began. On admission 10 days later she showed a good normal colour. There were no palpable abdominal swellings, and, apart from a doubtful low-grade pyrexia, no other clinical abnormalities. The urine contained a moderate amount of blood, a little pus, and a growth of *E. coli*. The blood urea was 37 mg./100 ml. As shown in Table I, she had a moderate polycythaemia.

TABLE I.—*Haematological Findings*

	Hb %*	R.B.C. Millions	Haemato-crit (%)	Retic. %	W.B.C.	Platelets
May 23	133	6·6	65			
,, 27	136	—	—			
,, 29	130	6·5	63	1·0		120,000
,, 30	133					
,, 30			Nephrectomy			
,, 30	104					
,, 31	101					
June 7	96				5,000	
July 16	96				6,000	
Jan. 30	108	4·7	45	<1	7,000	
May 5	118	5·7	50	<1	7,000	
June 6	109	5·3	45	<1	5,000	
,, 26	103	4·7	44	<1	6,000	

* Estimated by the M.R.C. Grey Wedge photometer. (100% = 14·8 g.)

Cystoscope, pyelograph, and straight abdominal *x*-ray film indicated a right renal growth. On May 30—that is, 18 days from onset of symptoms—nephrectomy was performed, and a tumour of the upper pole of the kidney was confirmed. No enlargement of the spleen or other abnormality was observed. Recovery was comparatively uneventful, and she has remained well during the subsequent year.

The haemoglobin fell to normal within a few hours after operation, and has remained so during the subsequent year.

The Tumour.—The right kidney had, replacing the upper pole, a moderate-sized round mass, lumpy, and of varied colour. Blood-vessels were not especially prominent in the capsule. The cut surface was a variegated red, yellow, or translucent—in fact, it was a typical renal carcinoma. Microscopically the appearance was of a well-differentiated clear cell growth. A number of blocks from different areas had a similar appearance. The adjacent kidney showed no unusual feature.

Previous cases of renal carcinoma recorded in this hospital group over the last 10 years were listed. In none of the 15 on record was there polycythaemia. The sections were examined and compared with the present case. The stains used were haematoxylin and eosin, Masson's trichrome, periodic acid Schiff, and aldehyde fuchsin. A proportion were of clear cell type, similar to the present case, and no feature distinguishing this case could be found.

COMMENT

The diagnosis of renal carcinoma accompanied by polycythaemia has been reported in 38 cases (Table II). The growth has in most reports been confirmed by microscopy. Where described, this is mostly given as

typical hypernephroma of clear cell type, the others being papillary or anaplastic hypernephroma. No features have been found to distinguish cases with polycythaemia from those without.

Polycythaemia vera was considered by Damon *et al.* (1958) to be present in one of their cases, and, judged by an enlarged spleen, raised white cells, or platelets, it might be diagnosed in two or three other cases.

Polycythaemia occurs in some 3% of cases of renal carcinoma (Conley *et al.*, 1957; Damon *et al.*, 1958), an incidence scarcely likely to be coincidental. The first haemoglobin in a series of cases of renal carcinoma given by Conley *et al.* shows a similar distribution to our cases.

20% of non-polycythaemic cases have a haemoglobin greater than 14.8 g., which in a malignant disorder accompanied very likely by haematuria suggests the possibility that, in some, polycythaemia may be masked by factors tending to produce anaemia.

Nephrectomy was carried out in 16 cases, and in all but two was followed by a return of the haemoglobin to normal. Some, however, were followed for a short period only and some had other factors possibly contributing to the remission, but in others there was good evidence of remission and that this was due to nephrectomy. In one a recurrence was associated with the reappearance of renal carcinoma (Forssell, 1946, 1947). It seems clear, therefore, that polycythaemia is secondary to the renal carcinoma in some cases at least.

Carnot and Deflandre (1906) suggested that they had demonstrated in the plasma, after haemorrhage, a hormone causing erythropoiesis. Recent work, notably that of Jacobson *et al.* (1957), may reasonably be said to have established a hormone erythropoietin. Their work points to the kidney as the source, for only in rats with kidneys removed did activity fail to appear in the plasma after stimulus. It seems to be increased after haemorrhage and in secondary polycythaemia.

C. W. Gurney and E. Goldwasser (1959, personal communication) report that, while the evidence is scanty, some hypernephromas are accompanied by elevated plasma erythropoietin. In our own case this has been estimated only since nephrectomy, and, as expected, appears to be within normal limits.

Polycythaemia is reported with other renal lesions (Forssell, 1958; Damon and Holub, 1958), as well as with tumours elsewhere (see Conley *et al.*, 1957). It is apparent that further work will be needed before one can accept the hypothesis that in renal carcinoma with polycythaemia we are dealing with primary oversecretion of erythropoietin.

I am indebted to Dr. W. H. James and Dr. J. M. S. Whiting for permission to report this case; to Dr. R. W. Payne, of St. Thomas's Hospital, London, for kindly estimating the plasma erythropoietin; and to Dr. Eugene Goldwasser for permission to quote unpublished results.

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TABLE II.—*Cases of Renal Carcinoma with Polycythaemia*

Author	Country of Publication	Age and Sex	Hb	R.B.C. Mills.	W.B.C. Thousands	Platelets Thousands	Spleen Palpable	Post-nephrectomy "Remission"
Medvei (1934)	Austria	62 M	142%	8·0	12	—	+	
Fairley (1945)	Australia	48 M	20·4 g.	8·4	8	N	+	
Forssell (1946)	Finland	49 M	121%	8·3	N	673	0	Yes and recurred
,, (1947)	,,	50 M	114%	7·3	N	N	+	
,, (1958)	,,	71 F	128%	8·1	7	185	0	
,, (1958)	,,	66 M	109%	6·0	6	N	0	
,, (1958)	,,	65 M	129%	6·2	3	N	0	
,, (1958)	,,	57 M	132%	6·2	N	N	0	No
Lawrence (1955)	U.S.A.	55 M	21 g.	8·7	N	529	+	
,, (1955)	,,	56 M	23 g.	9·6	N	N	+	
,, (1955)	,,	57 M	22·4 g.	7·8	N	N	+	
Videbaek (1950)	Denmark	55 M	147%	8·7	8	302	0	
,, (1950)	,,	57 F	95%	6·9	70	760	+	
,, (1950)	,,	45 M	130%	10·6	5	100	0	Yes
Battle (1955)		56 M	20 g.	7·3	N	N	0	
,, (1955)		50 M	22 g.	7·7	N	N	0	,,
,, (1955)		49 M	20 g.	8·9	N	N	0	,,
Gros (1955)	Germany	53 M	—	7·5	7	160	—	,,
Moe (1956)	Norway	55 M	140%	7·2	7	514	0	
Sjöberg (1957)	,,	60 M	124%	6·0	N	—	0	
Herbeuval *et al.* (1957)	France	45 M	165%	7·4	8	250	+	
Conley *et al.* (1957)	U.S.A.	61 M	17·6 g.	7·2	5	210	0	
,, (1957)	,,	32 M	20·5 g.	8·6	9	280	0	No
,, (1957)	,,	54 M	19·6 g.	6·5	12	282	0	Yes and recurred
,, (1957)	,,	46 M	—	7·0	5	170	0	
Campbell *et al.* (1958)	,,	65 M	23 g.	7·7	N	750	—	Yes
Frey (1958)	,,	63 M	19·6 g.	6·4	5	—	+	,,
Damon *et al.* (1958)	,,	49 M	22·4 g.	9·7	15	437	+	
,, (1958)	,,	40 M	22·5 g.	8·0	7	198	0	
,, (1958)	,,	59 M	20·0 g.	8·2	9	202	0	,,
,, (1958)	,,	54 M	125%	7·4	7	280	0	
,, (1958)	,,	67 F	19·0 g.	7·2	9	190	0	,,
,, (1958)	,,	72 M	18·0 g.	6·2	15	370	+	,,
,, (1958)	,,	70 M	18·7 g.	6·3	5	—	0	
,, (1958)	,,	59 M	23·2 g.	9·0	8	140	0	,,
,, (1958)	,,	58 F	20·5 g.	6·2	10	134	0	
,, (1958)	,,	69 M	17·5 g.	8·8	7	493	0	,,
Present case	Britain	73 F	133%	6·6	—	120	0	,,

Identical Twins : Death from Rupture of Dissecting Aneurysm of Aorta

Medial necrosis of the aorta is characterized by the deposition of basophilic acellular material in the media with subsequent degeneration of the elastic tissue and muscle fibres. Cyst formation is occasionally present. Although the condition is a common incidental finding at necropsy its importance lies in its predisposition to the development of a dissecting aneurysm. With weakening of the vessel wall splitting of the intima tends to occur, allowing blood to track into the degenerate media. Rupture may then take place into the peritoneum, pericardium, or pleura, or into the mediastinal or retroperitoneal spaces. On rare occasions the blood tracks back into the main lumen and organization may allow natural cure.

There seems to be no direct association with systemic disease or degenerative processes, but the condition is more common in men and usually occurs between the ages of 45 and 55. As related conditions cardiac hypertrophy, nephrosclerosis, and hypertension are often present. The clinical picture closely resembles that of coronary occlusion, and in the absence of post-mortem examination it is probable that many dissecting aneurysms are missed. This contention is supported by the relatively high frequency of such findings in medico-legal practice.

Death in identical twins from rupture of dissecting aneurysm of aorta at an interval of three years is described. The patients were born in 1905 of parents who survived to later life. Both men were employed in a clerical capacity ; both were married, with one child.

CASE 1

The patient was a healthy man with no history of trouble apart from migraine. In 1955 at examination for life insurance he was found to have a minor degree of hypertension, but had had no specific treatment for this condition.

On September 24, 1955, while painting a ceiling of his home he had severe pain in the chest. Within a matter of two hours he was admitted to hospital with a diagnosis of coronary thrombosis. He was regarded as suffering from coronary disease, though cardiograms at four-day intervals did not show any marked abnormality. He was treated with sedatives and anticoagulants, and appeared to be progressing satisfactorily until 10 days later, when he suddenly collapsed and died.

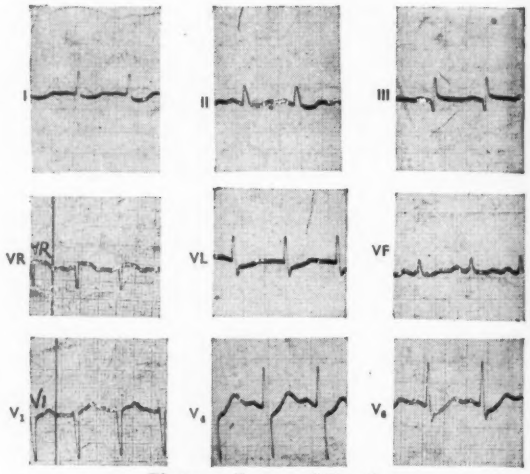
Post-mortem Examination (October 4).—Thorax: No adhesions ; the right sac contained a quantity of firm red blood-clot. Aorta: A small tear 1 cm. in length was found in the left side of the descending aorta at junction with the arch ; the adventitia had been perforated, with escape of blood into the right pleural sac ; there was extensive dissection of the aorta to below the diaphragm ; no evidence of syphilis or of atheroma was seen. Heart: Valves normal ; coronary arteries patent ; weight 370 g. Lungs: Well-marked atrophic emphysema ; no pneumonic change.

Histology.—Well-marked cystic degeneration, elastic laminae showing elongated slit-like cavities. There was adherent blood-clot on the outer side of the muscular coat.

CASE 2

The patient was a healthy man with no history of any significant illness. In 1955, after the death of his twin brother, he was anxious about himself, and sought reassurance that he was not likely to suffer a similar fate. He was then found to be fit apart from a minor degree of hypertension ; blood-pressure 150/100. No treatment was thought necessary for this condition. Thereafter he remained fit, though on occasion complaining of dyspepsia.

On October 12, 1959, while reaching up to a shelf in his office he had sudden severe chest pain. He felt faint and sweated freely, but was able to travel home by train unaccompanied. Some four hours after the onset of pain he was admitted to hospital with a diagnosis of coronary thrombosis. He was treated with sedatives and anticoagulants. On the day after admission an electrocardiogram suggested posterior subendocardial ischaemia, which in the light of the post-mortem findings was probably due to failing circulation through an atheromatous posterior coronary vessel (see Fig.). His condition steadily deteriorated, and with the development of right basal chest signs accompanied by a steadily falling blood-pressure the diagnosis became apparent. He died on the third day of illness.



Electrocardiogram of Case 2.

Post-mortem Examination (October 16).—Thorax: The right pleural cavity contained a large quantity of blood and the right lung was moderately collapsed ; blood-clot was present in the posterior mediastinum. Aorta: A dissecting aneurysm was present extending from the beginning of the thoracic aorta down to its bifurcation ; a tear 1.5 cm. long was present in the media just below the origin of the left subclavian artery. Heart: The left ventricle was slightly hypertrophied, the heart weighing 360 g. ; the right coronary artery showed moderate atheroma.

Attention is drawn to the close similarity of mode of onset, progress, and necropsy findings.

I thank Dr. N. F. Coghill, consultant physician, West Middlesex Hospital, for access to notes on Case 1, and Dr. Graham Hayward, cardiologist, Southend General Hospital, for records of Case 2.

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A new British Standard for anaesthetic breathing bags made of anti-static rubber (B.S.3353:1961) is one of a series of standards for anaesthetic equipment which are concerned with interchangeability of fittings, size designation, and safety. Adequate anti-static properties are specified for breathing bags, and it is stipulated that the necks of the bags shall fit properly on to mounts of standard size and shape (to be specified in a future British Standard for breathing attachments of anaesthetic apparatus). The standard also requires that the sizes of breathing bags shall be designated by the nominal capacity in litres and recommends a range of preferred sizes. Copies of the standard may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 3s. each. (Postage extra to non-subscribers.)

Reviews

CONCEPTION AND CONTRACEPTION

The Rhythm Way to Family Happiness. By John P. Murphy, M.D., and John D. Laux, M.B. (Pp. 200; illustrated. 18s.) London: Staples Press. 1959.

Marriage and Periodic Abstinence. By J. G. H. Holt, M.D. (Pp. 86+x. 10s. 6d.) London: Longmans. 1960.

The Condom as a Contraceptive. By Christopher Tietze, M.D. (Pp. 44.) New York: National Committee on Maternal Health, Inc. 1960.

Practical Birth Control Methods. By Abraham Stone, M.D., and Norman E. Himes, Ph.D. English edition, revised by Margaret C. N. Jackson, M.B., B.S., D.Obst.R.C.O.G., J.P. (Pp. 208; illustrated. 21s.) London: George Allen and Unwin, Ltd. 1960.

Law for the Rich. A Plea for the Reform of the Abortion Law. By Alice Jenkins. Introduction by Glanville Williams, LL.D., F.B.A. (Pp. 95. 15s.) London: Victor Gollancz. 1960.

Children for the Childless. Edited by Morris Fishbein, M.D. (Pp. 210+xiii. 12s. 6d.) London: Heinemann. 1960.

Books on how and how not to have children appear with a regularity which vies with that of ovulation. The relative constancy of ovulation in relation to the next menstrual period offers *The Rhythm Way to Family Happiness* to those who have religious or conscientious objections to other forms of contraception. This book explains the method in simple terms and consists almost entirely of charts and tables to indicate which are "baby days" and which are safe periods, according to the particular menstrual cycle of any woman. To help her calculate her menstrual habit and infertile phases there are pages on which the patient can keep records for nine years (with special provision for leap years!).

Those who prefer text to tables can turn to *Marriage and Periodic Abstinence*, which has been translated from the original Dutch. It tells the same story, but describes the various methods whereby the time of ovulation can be diagnosed or predicted, and does not depend entirely on mathematical calculations. It also makes considerable reference to the medical literature on which modern knowledge of ovulation is based, and therefore perhaps makes more suitable reading for the doctor than the patient. As such it is a restatement of established views and contains nothing new.

The "physiological" method of contraception is a little hard on some couples. According to Drs. Murphy and Laux, when the menstrual cycle varies from 20 to 30 days, only three or four days may be "safe." Those couples who desire a more reliable and more widely applicable technique for family limitation may therefore turn to *The Condom as a Contraceptive.* Although the title is unpromising, this paper-backed monograph is extraordinarily interesting. After a brief account of the history of the condom, the author discusses the present-day methods of manufacture, testing, storage, and costing of different types of rubber appliances. He reckons that the actual cost for making and testing one condom in the U.S.A. is no more than a half-cent, yet the consumer has to pay fifty times this amount. From this it is argued that well-organized manufacture and distribution in bulk could make the condom a cheap as well as efficient means of controlling population. This small booklet is also interestingly informative on other matters, such as the relative reliability of condoms and the extent to which they are used in different countries and by members of different religions. The general conclusion is that the condom may prove to be a highly acceptable, effective, and practicable method of contraception in many areas of the world.

But clearly the condom is not the best contraceptive in every circumstance, and other techniques, good and bad, are reviewed in *Practical Birth Control Methods.* In this the authors present an orthodox picture for the lay reader—a little history, sociology, anatomy, and physiology, followed by an account of different methods with their advantages and disadvantages. It is all simple yet up to date, and reference to modern oral contraceptives is commendably cautious. The final chapters are concerned with sterility and sterilization, and the English edition makes reference to the work of the Family Planning Association. The appendices give guidance as to where help can be obtained in different localities in this country, and as to what further books can be read.

And when contraception fails should abortion be induced? *Practical Birth Control Methods* includes a brief survey of induced abortion, its frequency, indications, and dangers, and one of its sections begins: "It is beyond dispute that the law concerning abortion in the United Kingdom is in need of repair." Unfortunately for the Abortion Law Reform Association nothing was ever less free from dispute. Hence their loud protestations, which are now voiced by Mrs. Alice Jenkins in *Law for the Rich.* She would not only have abortion positively legalized for medical reasons but would extend the indications to cover eugenic and social considerations. Her well-intentioned advocacy is based on the usual superficial emotional arguments, and on misrepresentation or disregard for the experience of legalized abortion in other countries. If there is a case for amendment of the law, it will not be strengthened by this book.

And while most couples are concerned to avoid pregnancy, or to limit their families, there are many who are disappointed at having no children or only one child, or at having to wait long for the desired pregnancy. Dealing with this problem still represents not less than 10% of gynaecological practice. *Children for the Childless* sets out a broad picture of fertility and infertility and of the factors which govern these. The book is authoritative, and contributors include many eminent names in the fields of gynaecology and social medicine, the preface to the English edition being by Mr. John Stallworthy. The matters discussed cover a wide range—family relationships; premarital sex instruction and examination; psychological reactions to fertility and infertility; heredity; the causes, investigation, and treatment of childlessness; artificial insemination; and adoption. All are explained in simple terms for the lay reader, and, even if the bias is towards the conditions obtaining in the U.S.A., many couples in Great Britain will find the book both interesting and valuable in helping them to understand or to become reconciled to their particular problem.

If the having and not having of children could be settled by means of books, they and all their allied problems would have been solved long ago. Unfortunately, or fortunately, they involve issues which arise from fundamental human desires, instincts, and relationships, ones which involve community as well as personal ethics and needs, ones which the individual cannot always view dispassionately and scientifically. Where they are detached and factual the particular books mentioned here all have something to offer by way of

education of the individual; otherwise they leave the basic moral, social, and personal problems as delightfully obscure and controversial as ever.

T. N. A. JEFFCOATE.

ASPECTS OF SURGERY

Surgical Aspects of Medicine. Edited by H. Daintree Johnson, M.A., M.B., B.Chir., F.R.C.S. (Pp. 382+21+xv; illustrated. 65s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

This is an interesting and unusual book. It sets out to explain to physicians and general practitioners the indications for surgical treatment, the methods by which this treatment can be carried out, and the results which may be expected.

Like all multiple-author books (there are included sections by forty writers) the quality varies from chapter to chapter. Some have written their sections as essays, which are a joy to read; others have adopted a formal textbook approach. The field covered is a wide one—in fact, all those conditions in which the indications for surgical treatment have to be weighed in the balance. It may be invidious to mention particular chapters, but those which struck the reviewer as outstanding were the ones on haemorrhoids, gall-stones, acute abdominal diseases in childhood, cancer of the lung, the Rhesus factor, the nodular breast, neckache and backache, and minor injuries. However, there are many other good chapters, particularly those dealing with the special senses.

There is little to criticize. In dealing with prostatic enlargement it is unfortunate that the modern methods with a Gibbon catheter and closed drainage, by which infection can be eliminated in the majority of cases, find no mention. Also, concerning Raynaud's disease, the recent work on vascular control, as a result of which symptoms can nearly always be relieved without sympathectomy, is not mentioned. It is odd to find spider naevi and Campbell de Morgan spots classified as birthmarks. Rammstedt's name is incorrectly spelt.

The book, on the whole, well fulfils its purpose. In these days of specialization there is much that the surgeon will find to interest him outside his own particular branch, and it can confidently be recommended to this wider field for whom it is specially written.

R. MILNES WALKER.

PROGRESS IN CANCER

Cancer. Progress Volume, 1960. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. (Pp. 242+xv+16; illustrated. 60s.) London, Toronto, Sydney, Wellington, Durban: Butterworths. 1960.

A *Progress Volume* dated 1960 has been issued as a sequel to the six volumes already published entitled *Cancer*, and this, like the preceding volumes, has also been edited by Mr. Ronald W. Raven. To this progress volume there are no less than thirty-six contributors, and the ground covered is almost unlimited, including experimental research, general pathology, statistics, clinical aspects, radiotherapy, and chemotherapy.

Most of the authors who have been invited to contribute to this book are from English-speaking countries, but they include also one French and two Russian contributors. One of the Russians, Dr. N. I. Lazarev, has a chapter on new developments in the hormone therapy of malignant tumours, and the other, Dr. L. F. Larionov, has written on the subject of alkylating metabolites and also on progress in the chemotherapy of solid tumours. Professor Marcel Dargent, the French contributor, has an interesting chapter on progress in the diagnosis of cancer.

In a book such as this, in which each author is an acknowledged expert, it seems invidious to select individuals for special mention, but it would be good advice to the general reader to begin at the beginning, because the first chapter by Dr. R. J. C. Harris is a masterpiece in its account of recent advances in tumour virology. This chapter, and many of the others, is followed by a long list of references to work published in the last three or four years, thus greatly adding to the value of the book as a work of reference.

If it is the intention of Mr. Raven and the board of advisory editors to produce a progress book like this each year, they will be rendering a great service both to cancer research workers and to clinicians interested in the chemotherapy and radiotherapy of malignant disease.

CUTHBERT E. DUKES.

LEUKAEMIA

Leukemia Cutis. By Samuel M. Bluefarb, B.S., M.D., F.A.C.P. With an introduction by Marcus R. Caro, M.D. (Pp. 489+xxvi; illustrated. £7 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Not only dermatologists will be grateful to Dr. Bluefarb for this exhaustive work on leukaemia, which will be acknowledged as a standard book of reference. The dermatological aspect of the problems presents, more dramatically than other aspects, the great diagnostic, prognostic, and therapeutic difficulties encountered in the diseases covered by the label of leukaemia and its protean manifestations. Dr. Bluefarb has undertaken the task of digesting the world literature (there are 761 references) and presenting a synopsis of the experience and opinions of others, to which he adds his own considerable experience.

The broad aspects are well presented and are illustrated by innumerable case reports from the literature. There is still dispute about the origin of the disease in particular clinical entities but general agreement on the common ultimate origin from the "stem cell," and the term "stem-cell leukaemia" is sometimes employed when it is difficult to differentiate a particular type. It is calculated that the incidence of leukaemia is five times greater now than it was in 1900. It is also stated that the incidence in blood relations of a patient with leukaemia is seventeen times as great as in control groups. The incidence in radiologists and dermatologists is significantly high.

The specific lesions of the different types of leukaemia are well described, and the variable courses the disease may take are well illustrated by case reports. There are full and valuable descriptions of the many and varied non-specific clinical features commonly seen in leukaemia, with emphasis on their importance for early diagnosis, and there is full discussion of differential diagnosis. The black-and-white illustrations throughout the book, however, are of poor quality and quite unhelpful, which is unfortunate in an otherwise excellent production. The question of prognosis is always difficult and individual in this disease, and is only dealt with briefly. Review of treatment similarly follows conventional lines. Treatment remains unsatisfactory in the majority of cases.

The author takes some particular aspects of the field which have interested him and deals with them at length, as the association of leukaemia with haemorrhage, with herpes zoster, exfoliative dermatitis, polycythaemia vera, and a number of other non-specific manifestations. Many would have welcomed fuller expression of the author's views on many points, but in the main he presents the views of other authorities. There is a good chapter on diagnosis, well illustrated, by Drs. Freedman and Leithold, with description of laboratory techniques.

J. T. INGRAM.

ANGIOCARDIOGRAPHY ATLAS

Atlas der Angiokardiographie Angeborener Herzfehler. By Dr. Ralph Künzler and Dr. Nikolaus Schad. Foreword by Professor Dr. Guido Franconi and Professor Dr. Max Grob. (Pp. 224+xii; illustrated. DM. 85.) Stuttgart: Georg Thieme Verlag. 1960.

The authors are to be congratulated on producing a concise, well-illustrated and well-documented book on angiocardiography. The illustrations, in atlas formation, are of a very high standard and cover the subject very well. This book can be heartily recommended to all those who are interested in the subject.

J. W. MCLAREN.

UNEQUAL LEGS

Surgical Treatment of Unequal Extremities. By Charles Weer Goff, M.D. (Pp. 184+ix; illustrated. 88s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

This valuable monograph is one of the *American Lecture Series*, and reviews the causes, methods of investigation, and treatment of short limbs. Discrepancies of an inch or so in the length of adult lower limbs can generally be disguised by simple modifications of both shoes, but above an inch unsightly shoe-wear may be necessary. To treat this loss in childhood, much surgical ingenuity has been exercised—often with relative failure to observe the biological conditions underlying the defects of limb growth and repair.

The value of the present work is in its presentation of studies in these biological problems and of the methods used for many years by the author and his associates at the Newington Hospital for Crippled Children in Hartford, Connecticut. In the main it is a tribute to T. Wingate Todd (who carried out fundamental studies in bone maturation and, based upon the ossification of the carpus, drew up an atlas of "bone ages"), to W. T. Green and M. Anderson (who, upon this, prepared charts of predictable limb growth), and above all to Walter Blount (who has gone so far in making epiphysial arrest in a longer limb a safe and controllable procedure). The work also surveys the world literature on this fascinating subject, but strangely makes little mention of British work, which is almost dismissed as Procrustean: F. G. Allan's careful work is not mentioned, and Hey Groves is only referred to incorrectly in the bibliography. For some reason Trueta is credited with what surely must have been the everyday observation of generations of surgeons: that osteomyelitis often stimulates bone growth. Another strange thing is that there is no reference to the arrest of metaphysial growth which is found in children being treated for tuberculosis of the hip. This is an error made in many works now published in the English-speaking world. Because we do not see skeletal tuberculosis in children, we should not forget how big a problem this is in many less highly organized communities. With these few carping criticisms we nevertheless are full of admiration for the great mass of information here gathered together and so beautifully produced.

NORMAN CAPENER.

PULMONARY SUPPURATION

Les Suppurations Bronchiques, Pulmonaires et Pleurales. By Raoul Kourilsky and Guy Decroix. (Pp. 259; illustrated. No price.) Paris: J.-B. Baillière et Fils. 1960.

Professor Kourilsky has been interested in suppuration of the bronchi, lungs, and pleura for more than 30 years. This book, written principally by one of his collaborators, expresses his views, and its purpose, modestly described in the preface, is no more than that it should be useful.

Three main topics are presented—namely, purulent bronchitis and bronchiectasis, pulmonary suppuration and lung abscess, and empyema thoracis. In common with French practice, the importance of bronchial intubation is repeatedly stressed. Diagnostic bronchoscopy and the insertion of antibiotics through catheters are recommended far more often than is usual in British clinics. Pulmonary suppuration was noted frequently to be associated with malnutrition and chronic alcoholism, which partly accounts for the inclusion in the routine treatment of such measures as blood transfusions of 100–200 ml. twice a week, intravenous ascorbic acid daily for a fortnight, calcium, vitamin B, phosphoric acid, and sedatives. Orthodox opinions are expressed upon radiology, bacteriology, and antibiotic therapy.

With suppuration as the only common feature of these somewhat unrelated conditions, readers are entitled to expect a discourse upon the factors which predispose and contribute to the formation of pus within the thorax. Instead, they find routine descriptions which could be more appropriately accommodated in a text-book upon respiratory diseases. A book of this size could easily have been devoted to any one of these three topics, and would have given the authors an opportunity of expressing themselves more fully. As it stands, its appeal is limited. The specialist is likely to find little which is new or with which he disagrees; the general reader may care to refresh his memory of modern diagnostic and therapeutic measures in this rather incongruous medley of diseases. The style of writing is concise and the illustrations are clear. The bibliography is slipshod.

N. C. OSWALD.

CLINICAL ANATOMY

Clinical Anatomy. A Revision and Applied Anatomy for Clinical Students. By Harold Ellis, M.A., M.Ch.(Oxon.), F.R.C.S. (Pp. 369+xvi; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

The aim of the author of this book is to attempt to bridge the gap in anatomical knowledge which he believes exists between what students are taught in the department of anatomy and what may be regarded as of clinical importance. It is doubtful whether this book will fulfil the need that the author intended. It can be said at once that there is nothing new in the way that the facts have been presented.

The book is subdivided into the following sections: the thorax; abdomen and pelvis; upper limb; lower limb; head and neck; and central nervous system. There are many vague and inaccurate statements. On p. 68 the author describes the suspensory ligament of Treitz as coming from the left crus of the diaphragm,

whereas in fact it arises from the right crus. On p. 83 he states, "At an early stage rapid proliferation of the gut wall obliterates its lumen and this is followed by subsequent recanalization." This is not in accordance with the facts. It is true that the lumen of the second part of the duodenum at the site of origin of the bile duct may be obliterated, but not the lumen of the entire gut. On p. 99 he states, "Occasionally the kidney will fail to migrate caudally, resulting in a persistent pelvic kidney." This, of course, should be cranially.

Many of the diagrams are misleading. In Fig. 47 the prostate is shown as too small. Again in Fig. 48 the level of the tip of the coccyx is too low; with the individual in the upright position the tip of the coccyx is approximately at the level of the upper surface of the symphysis pubis. Many other figures—for example, Figs. 81, 85, and 180 B—are entirely misleading. In Fig. 81 the infundibulo-pelvic ligament is shown as arising from the anterior aspect of the broad ligament. In Fig. 180 B the position of the mylohyoid line is wrong.

The author of this volume is probably not in close touch with what is taught in modern departments of anatomy. In many departments, while the surgical aspects are not stressed, and rightly so, those aspects of anatomy which are of importance in medicine are brought to the students' notice.

W. J. HAMILTON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Surgical Diseases of the Pancreas. By John M. Howard, M.D., F.A.C.S., and George L. Jordan, jun., M.D., M.S., F.A.C.S. (Pp. 607+xviii; illustrated. £7 7s.) London: Pitman Medical Publishing Co. Ltd. 1960.

Clinicopathological Conferences of the Massachusetts General Hospital. Selected Medical Cases. By Benjamin Castleman, M.D., and H. Robert Dudley, jun., M.D. (Pp. 295+xiv; illustrated. 90s.) London: J. and A. Churchill, Ltd. 1960.

Dr. Eurich of Bradford. By Margaret Bligh. (Pp. 295. 25s.) London: James Clarke and Co. Ltd. 1960.

Pain. By F. J. J. Buytendijk. Translated by Eda O'Shiel. (Pp. 189. 25s.) London: Hutchinson. 1961.

The Surgery of Mitral Stenosis. By Robert P. Glover, M.D., M.S.(Surg.), F.A.C.S., F.A.C.C., and Julio C. Davila, M.D., F.A.C.S., F.A.C.C. (Pp. 219+xii; illustrated. $9.50.) New York and London: Grune and Stratton. 1961.

Louis Pasteur. A Master of Scientific Enquiry. By Jacques Nicolle. (Pp. 196. 35s.) London: Hutchinson. 1961.

Lettres de Théodore Schwann. Edited by Marcel Florkin. (Pp. 274; illustrated. Fr. 250.) Liège: Société Royale des Sciences de Liège, Université de Liège. 1961.

Krebskrankheit und berufliche Rehabilitation. By Dr. med. Corneliu Popescu. (Pp. 121+viii; illustrated. DM. 17.70.) Jena: Veb Gustav Fischer Verlag. 1961.

Introduction to Medicine and Medical Terminology. By Louise Espey Bollo, A.B. (Pp. 356+vii. 35s.) Philadelphia and London: W. B. Saunders Company. 1961.

Surgical Urology. By R. H. Flocks, M.D., and David Culp, M.D. Second edition. (Pp. 441; illustrated. 79s.) Chicago: The Year Book Publishers, Inc. 1961.

Family Needs and the Social Services. (Pp. 233+xi. 30s.) Published by George Allen and Unwin Ltd. for Political and Economic Planning, Queen Anne's Gate, London S.W.1. 1961.

The Year Book of Drug Therapy. Edited by Harry Beckman, M.D. (Pp. 587; illustrated. 64s.) Chicago: The Year Book Publishers, Inc. 1961.

Georg Thieme Verlag, Stuttgart, Verlagsverzeichnis 1946-61. Medizin, Naturwissenschaften. (Pp. 303. No price.) Stuttgart: Georg Thieme Verlag. 1961.

Occasion for Ombudsman. By T. E. Utley. (Pp. 160. 15s.) London: Christopher Johnson. 1961.

Dermatology. Diagnosis and Treatment. By Marion B. Sulzberger, M.D., F.A.C.P., Jack Wolf, M.D., and Victor H. Witten, M.D. Second edition. (Pp. 615; illustrated. £5 5s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1961.

Biological Problems Arising from the Control of Pests and Diseases. Symposia of the Institute of Biology, No. 9. Edited by R. K. S. Wood. (Pp. 116+viii. 25s.) London: The Institute of Biology, 41 Queen's Gate, S.W.7. 1960.

Clinical Use of Radioisotopes. A Manual of Technique. Edited by Theodore Fields, M.S., F.A.C.R.(Assoc.), and Lindon Seed, M.D. Second edition. (Pp. 475; illustrated. 79s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1961.

The Sexual Side of Marriage (Handbook of Marriage). By E. Parkinson Smith. (Pp. 95+viii. 3s. 6d.) London: Pedigree Books.

Living Ability. Quantitative Measurement, Establishment of the True Scientific Basis of Medicine and Actual Application (Intelligibly Demonstrated). By G. Pantel, M.D. (Pp. 109. No price.) London: The Whitefriars Press Ltd. 1958.

Control of Malnutrition in Man. Prepared by the Subcommittee on Control of Nutritional Diseases and authorized for publication by the Committee on Evaluation and Standards of the American Public Health Association. (Pp. 140+vi. No price.) New York: American Public Health Association, Inc. 1960.

Trends in Juvenile Delinquency. By T. C. N. Gibbens. (Pp. 56. 3s. 6d.) Geneva: World Health Organization. London: H.M. Stationery Office, S.E.1. 1961.

Aspects of Public Health Nursing. By various contributors. (Pp. 185. 8s. 6d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1961.

The Psychoanalytic Study of the Child. Volume XV. Managing Editors: Ruth S. Eissler, M.D., Anna Freud, LL.D., Heinz Hartmann, M.D., and Marianne Kris, M.D. (Pp. 481. 50s.) London: The Hogarth Press. 1961.

Fundamentals and Possibilities in Anti-Tuberculosis Vaccination. By Richard Prigge, M.D., D.h.c., and Günther Heymann, M.D. Translated by H. Chandler Elliott, Ph.D. (Pp. 105+vi. 40s.) London: Oxford University Press. Toronto: University of Toronto Press. 1960.

World Directory of Venereal-Disease Treatment Centres at Ports. Second edition. (Pp. 164. 8s. 6d.) Geneva: World Health Organization, Palais des Nations. London: H.M. Stationery Office, P.O. Box 569, S.E.1. 1961.

Die Intersexualität. Edited by Dr. Claus Overzier. (Pp. 560+xv; illustrated. DM. 119.) Stuttgart: Georg Thieme Verlag. 1961.

The Structure of the Eye. Proceedings of the Symposium held April 11-13, 1960, during the Seventh International Congress of Anatomists, New York. Edited by George K. Smelser. (Pp. 570+xv; illustrated. £5 7s. 6d.) New York and London: Academic Press Inc. 1961.

Protection Against Radiation. A Practical Handbook. By John D. Abbatt, M.B., Ch.B., D.M.R., J. R. A. Lakey, Ph.D., B.Sc., A.Inst.P., and D. J. Mathias. (Pp. 235+viii; illustrated. 25s.) London: Cassell. 1961.

Pneumoconiosis—Modern Trends. Report of meetings held in Birmingham (April, 1959) and in Glasgow (January, 1960). (Pp. 144; illustrated. 12s. 6d.) London: Chest and Heart Association, Tavistock House North, Tavistock Square, W.C.1.

Family Welfare Centre. By Nancy Lingard, Margaret Platt, M.B., Ch.B., D.P.M., and Barbara Oldham, M.B., Ch.B., M.R.C.S., L.R.C.P. (Pp. 44. 5s.) Available to social workers from the Family Welfare Centre, Darbishire House, Upper Brook Street, Manchester 13.

Gynäkologische Urologie. By W. Langreder. (Pp. 306+xii; illustrated. DM. 59.) Stuttgart: Georg Thieme Verlag. 1961.

Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. By Kurt Kolle. (Pp. 418+xi; illustrated. DM. 29.80.) Stuttgart: Georg Thieme Verlag. 1961.

Rorschach Psychology. Edited by Maria A. Rickers-Ovsiankina. (Pp. 483+xvi. 68s.) London: John Wiley and Sons Ltd. 1961.

Salmonella: Salmonella Infections. Bibliography of Literature. (Pp. 40+v. No price.) Washington: U.S. Department of Health, Education, and Welfare. 1960.

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TUBERCULOSIS AND RE-EMPLOYMENT

Modern methods of treating the tuberculous patient have made a remarkable alteration in the prognosis of this disease, giving him good prospects not only of restored health but of avoiding relapse and of maintaining efficiency at work. Provided the patient co-operates well and drugs in effective combination are administered for a sufficient length of time, virtual sterilization of the majority of the foci of disease is probable, though surgical excision may be needed in a small proportion of cases. If chemotherapy is continued for twelve months or more, few if any of the residual foci which represent former cavities yield viable tubercle bacilli on culture.[1 2] Conversion of positive sputum is usually effected in the majority of patients within a few months.[3] Provided sputum conversion has been attained, the patient under treatment is often fit to return to work while continuing to take chemotherapy. Indeed, with closed lesions of lesser extent the patient may well be able to be about and working from the start of treatment, or possibly after a brief period of adjustment to the drug regime.[4]

Relapse is rare after effective chemotherapy of at least a year's duration. In a large series of sputum-positive cases admitted to Edinburgh hospitals in 1953[5] relapse was reported in only 1% of patients treated for 12 to 18 months and in none of those treated for longer periods when surveyed three years later. J. Batten and colleagues[6] found that, in their series of 193 patients, eight with originally extensive disease relapsed after eighteen months' chemotherapy but all recovered, four without further treatment. The prolonged periods of rest in bed which were formerly considered desirable in the management of tuberculosis have been, with few exceptions, rendered unnecessary by modern treatment, and this is of great value in assisting an early return to work. A fresh view on the employment of ex-patients is therefore desirable.

The reception that ex-patients should receive when they seek re-employment and superannuation, life assurance, and emigration receives timely consideration in a recent report of the Joint Tuberculosis Council.[7] The council has collected many examples of difficulties regarding employment. It finds that a history of tuberculosis is often a handicap to promotion, to application for senior posts, and even to being put on a short list for employment. Some employers in industry still refuse to accept ex-patients for reasons which are not justifiable in the light of modern knowledge. The unwarranted fears of foremen or fellow employees are often made an excuse for rejection. At times or places where labour is short, obstruction to employment may be less severe, but difficulties tend to arise as soon as these conditions change. Fortunately many firms adopt an understanding attitude and are especially helpful to their employees who have undergone treatment, but there are still many who are unduly hesitant in taking back their own employees and even more in accepting a person who has had to change to a new employment. Government departments and local authorities seem more reluctant to employ ex-patients than do private employers.

Sometimes the requirement of contribution to a superannuation fund may raise problems, but, since an employee must usually work for ten years before pension rights are established, there is ample opportunity to demonstrate the good prognosis of the ex-patient. Another cause for rejection is a family history of tuberculosis; but the disease is not hereditary, and such a history has no relevance to a healthy individual's employability: this should be judged solely on the medical findings in the applicant.

The principal reason for taking care in employing the ex-patient is the risk of infecting others. Consequently those patients who have persistent open lesions and sputum containing tubercle bacilli need treatment; or, for the small proportion who can be employed, special conditions are required. These may be necessary also for the treated patient who has considerable residual disability though active disease has healed. But the successfully treated patient can usually return to his employment, or be suitably adjusted to another if the former is unduly arduous or stressful. Such patients can even be employed in food industries, for food is rarely, if ever, the conveyer of infection by human bacilli. Infection is conveyed from person to person and hence more care

[1] Stewart, S. M., Turnbull, F. W. A., and Macgregor, A. R., *Tubercle (Lond.)*, 1956, **37**, 388.
[2] Harrison, G. K., Large, S. E., Mackay-Dick, J., Reid, L., and Riddell, R. W., *Thorax*, 1959, **14**, 104.
[3] Thomas, H. E., *et al.*, *Lancet*, 1960, **2**, 1185.
[4] Tuberculosis Society of Scotland Research Committee, *Tubercle (Lond.)*, 1957, **38**, 375.
[5] Ross, J. D., Horne, N. W., Grant, I. W. B., and Crofton, J. W., *Brit. med. J.*, 1958, **1**, 237.
[6] Batten, J., Turner-Warwick, M., Hoyle, C., and Nicholson, H., *Lancet*, 1960, **1**, 409.
[7] *Tuberculosis: Report on the Reception of Ex-patients in Respect of Re-employment and Superannuation, Life Assurance and Emigration.* Copies from Dr. R. L. Midgley, Hawkmoor Chest Hospital, Bovey Tracey, Devon, price 1s.
[8] Cartwright, A., Martin, F. M., and Thomson, J. G., *Med. Offr*, 1958, **99**, 73.

is justifiable where susceptible persons such as infants and young persons may be exposed to a possible, if rare, risk. Teachers are usually required to show that they have been well and sputum-negative for at least six months before returning to the classroom, and this is a reasonable condition.

In general, the restrictions which have hindered the ex-patient from successful reinstatement in employment need to be reconsidered against the effectiveness of modern treatment. There is still an astonishing ignorance of the meaning of tuberculous infection and disease and of modern treatment among the general population.[8] As the council points out, chest physicians and general practitioners have opportunities of enlightening employers of this changed view, and assisting their patients in an early return to work. Prolonged absence for rehabilitation or special facilities for light or part-time work need be requested only in exceptional circumstances, and then the medical adviser should take especial care, by interview with the employer or in some other way, to clarify the position and explain why it is necessary.

MANAGEMENT OF PATIENTS WITH DISSEMINATED SCLEROSIS

The recent symposium on disseminated sclerosis at the Royal Society of Medicine[1] gave an insight into the efforts being made to discover the cause of the disease, though it still remains obscure. Until its pathogenesis is known, it is unlikely that a specific cure will be found. This is not to say that various treatments should not be tried, but it is difficult to assess the results in a disease whose course and prognosis varies so much from patient to patient. At any rate, much can be done to relieve the suffering of the individual.

In Newcastle upon Tyne H. Miller and his co-workers[2] have shown by a statistically controlled study that the results in three groups of patients treated for eighteen months with prednisolone, calcium aspirin, and dummy tablets were very similar. The appearance of acute exacerbations and new symptoms and signs with almost equal frequency in all three groups suggested that the activity of the disease continued uninfluenced by the drugs. For some years in Oxford H. V. Smith[3] has been treating cases of disseminated sclerosis by intrathecal P.P.D. (purified protein derivative of tuberculin). This often produces an acute exacerbation, but has been followed by a reduction in the frequency of the relapse rate and improvement in the patient's condition. On the other hand, Miller[4] found that his patients did not improve on P.P.D. treatment. Though patients and their relatives often press their doctor to prescribe the Russian vaccine, it is best not to do so, for G. W. A. Dick and colleagues have identified the organism as rabies virus.[5–7] There is little doubt that physiotherapy has much to offer the disabled patient. Assisted, passive, and resisted movements and walking exercises controlled by trained physiotherapists do much to reduce spasticity, control ataxia, and improve the patient's morale. It is important that the patient should not be exhausted by treatment, so the sessions should be frequent and short. If spasticity is so severe that physiotherapy has little effect, other measures may be necessary. Drugs such as quinine, mephenesin, and benztropine have been disappointing, but are worth trying. Recent reports[8–10] have suggested that phenol in glycerin or ethyl iodophenylundecanoate ("myodil") given intrathecally can reduce the spasticity in the lower limbs without interfering with bladder function. The patient who may be helped by this technique is the one whose spasticity is severe but with little loss of power; his gait may distinctly improve. Moreover, the pain associated with flexor spasms is relieved, though this effect wears off in time and the injection may have to be repeated; then even a higher concentration of phenol does not give so striking a result as followed the initial treatment.

In the late stages of the disease, when extreme degrees of paraplegia-in-flexion and adduction deformity of leg have developed, surgery may be required to deal with contractures. G. Platt and colleagues[11] advocate a combination of neurectomy, tenotomy, and tendon transplant. It should be emphasized that these procedures are largely undertaken to relieve painful spasms, to facilitate nursing care, and to allow the patient to sit with comfort.

D. McAlpine and colleagues[12] note the importance of rest during relapses, but when possible the patient should be encouraged to bear some weight every day if there is any spasticity in the legs. Weight-bearing will facilitate the extensor leg reflexes and counteract any tendency to flexor spasms, but if it is not possible the patient should lie prone for periods during the day. This position will also help to prevent pressure

[1] *Proc. roy. Soc. Med.*, 1961, **54**, 1.
[2] Miller, H., Newell, D. J., and Ridley, A., *Lancet*, 1961, **1**, 127.
[3] Smith, H. V., Espir, M. L. E., Whitty, C. W. M., and Russell, W. R., *J. Neurol. Neurosurg. Psychiat.*, 1957, **20**, 1.
[4] Miller, H., Communication given to the Association of British Neurologists, 1960.
[5] Dick, G. W. A., McKeown, F., and Wilson, D. C., *Brit. med. J.*, 1958, **1**, 7.
[6] Shubladze, A. K., and Dick, G. W. A., ibid., 1958, **2**, 245.
[7] Ibid., 1958, **2**, 214.
[8] Nathan, P. W., *Lancet*, 1959, **2**, 1099.
[9] Kelly, R. E., and Gautier-Smith, P. C., ibid., 1959, **2**, 1102.
[10] Liversedge, L. A., and Maher, R. M., *Brit. med. J.*, 1960, **2**, 31.
[11] Platt, G., Russell, N. R., and Willison, R. G., *Lancet*, 1958, **1**, 757.
[12] McAlpine, D., Compston, N. D., and Lumsden, C. E., *Multiple Sclerosis*, 1955, Edinburgh and London.
[13] Müller, R., *Acta med. scand.*, 1949, Suppl. 222.
[14] Tillman, A. J. B., *Ass. Res. nerv. Dis. Proc.*, 1950, **28**, 548.

sores. Bladder care is particularly important in the late stages of the illness; infection should be dealt with swiftly and resection at the bladder neck may be necessary if cystoscopy shows a bar. Male patients suffering from incontinence can obtain a portable urinal strapped to the thigh.

Factors such as trauma and infection may affect the course of the disease adversely.[12] Trivial febrile illnesses and minor trauma should be treated with care; ataxic patients should be careful to avoid falls and for this reason should be encouraged to carry sticks and use other walking-aids. The relapse rate is reported not to increase after surgical operations[1 12] or during pregnancy.[12–14] J. H. D. Millar[1] found an increase in relapses in the puerperium, but when the material was reviewed ten years later the clinical status of married women with children was no worse than that of single and married women without children. It would appear that when the disease is active and unstable, as in the early years, a relapse is more likely in the puerperium, but it becomes less so in the chronic phase of the illness. It seems desirable, if possible, to restrict pregnancy to a period of remission, ideally two years after a relapse. Disseminated sclerosis as such is not a reason for necessarily advising termination of pregnancy, but a pregnant patient should rest as much as possible during the last months of pregnancy and the puerperium.

There is a great need for trained social workers to advise and visit patients at regular intervals. It is surprising how few are aware that they are entitled to wheel-chairs and other benefits. A patient's comfort can be considerably increased by simple gadgets and aids in the home. Day centres for occupational therapy, physiotherapy, and social and recreational purposes would be ideal for the severely disabled who are unable to work or care for themselves; and possibly these centres could rehabilitate other patients and train them for suitable occupations. Severely disabled patients require short periods in hospital for treatment and to give their relatives a rest.

POLIOMYELITIS VACCINES THIS YEAR

A recent statement issued by the Ministry of Health on poliomyelitis vaccines[1] is of some importance. For the time being the inactivated vaccine (Salk type) is to remain the one provided and recommended for general immunization against poliomyelitis. A fourth dose is to be made available for children aged 5 to 11 years. This decision is long overdue but nevertheless welcome, though it seems unfortunate that restrictions on the use of vaccine should still exist. The sooner the vaccine is made generally available for people of all ages the better. Recent experience in the United States has shown only too clearly that paralytic poliomyelitis continues to cause trouble, as shown by outbreaks last year in Providence, Rhode Island, and in Baltimore.[2] As E. R. Alexander[2] and A. D. Langmuir[3] point out, these outbreaks have been largely confined to selected and isolated groups of poorly vaccinated or non-vaccinated persons. Less than 32% of the population in the United States under 40 years of age have received the recommended four doses, and of the age group 5 to 9 only 50%. In Great Britain we have an example of what can happen, for it is reported that of the 12 paralytic cases seen recently in the Ipswich area none had been vaccinated.[4]

The Ministry also made known certain decisions on the use of live oral vaccine which, in view of the present outbreak in East Anglia, are of topical interest. An oral vaccine of the three virus types has been produced in this country from seed virus made available by A. B. Sabin in Cincinnati. It will be kept in reserve for special circumstances. Despite the fact that live vaccines, including the Sabin, Koprowski, and Lederle strains, have been given on a vast scale (to over 70,000,000 people in many parts of the world) and a mass of information on them has been gained, a number of questions on dosage, spacing of doses, and length of immunity remain to be answered in the context of the British environment. It therefore seems a wise step to hold this vaccine for further investigation as an alternative in reserve while pressing ahead with the inactivated vaccine.

It is now just over 10 years since H. Koprowski and his associates[5] fed live attenuated type-2 virus (TN strain) to a 6-years-old boy and later to a further 19 susceptible children. This experiment established the basic principle that live vaccine given by mouth would set up symptomless intestinal infection with virus excretion in the faeces and development of type-specific antibody. Thus the process of immunization resembled, in every way, natural inapparent infection, as indeed it was intended to do. During the next few years Koprowski and his colleagues fed type 2(TN) and also a type-1 strain (SM) to about 500 children,[6]

[1] *Brit. med. J.*, 1961, **1**, 1167.
[2] Alexander, E. R., *J. Amer. med. Ass.*, 1961, **175**, 837.
[3] Langmuir, A. D., ibid., 1961, **175**, 840.
[4] *Brit. med. J.*, 1961, **1**, 1116.
[5] Koprowski, H., *Trans. and Studies*, College of Physicians of Philadelphia, 1960, **27**, 95.
[6] Koprowski, H., *et al.*, *J. Amer. med. Ass.*, 1956, **162**, 1281.
[7] Sabin, A. B., Communication to IX International Congress on Paediatrics, Montreal, 1959.
[8] Dick, G. W. A., *et al.*, *Brit. med. J.*, 1957, **1**, 65.
[9] Dane, D. S. *et al.*, ibid., 1957, **1**, 59.
[10] Dick, G. W. A., and Dane, D. S., ibid., 1957, **1**, 70.
[11] Paul, J. R., *New Engl. J. Med.*, 1961, **264**, 651.
[12] Murray, R., *J. Amer. med. Ass.*, 1961, **175**, 843.
[13] Sweet, B. H., and Hilleman, M. R., *Proc. Soc. Exp. Biol.* (*N.Y.*), 1960, **105**, 420.
[14] Hale, J. H., Lee, L. H., and Gardner, P. S., Fifth International Poliomyelitis Conference, 1960.
[15] Melnick, J. L., *et al.*, *J. Amer. med. Ass.*, 1961, **175**, 1159.

with essentially the same results. A. B. Sabin[7] showed clearly not only that live poliovaccine would produce a subclinical intestinal infection in the vaccinated but that the excreted virus could spread to others in close contact. Whether they became infected depended on their immune status. Those with solid natural immunity did not become infected; those with partial or no immunity became infected irrespective of whether they had received inactivated vaccine or not. Furthermore, it was found that, in addition to the development of circulating antibody in persons fed with live virus, the intestinal tract became resistant to reinfection. Unfortunately there was a snag, which was shown up by G. W. A. Dick and D. S. Dane in Belfast. They found that the virus excreted in the faeces after vaccination differed from the vaccine virus ingested, for an increase in virulence could be demonstrated in monkeys with both the TN and SN excreted strains.[8-10] These observations were to prove of fundamental importance in drawing attention to the necessity of selecting the most suitable strains for oral vaccines. There has been much argument about the correlation of monkey neurovirulence with virulence for man, but the experience of the past few years shows there is a good case for selecting strains which have a low virulence when injected into monkeys by intraspinal, intracerebral, and intramuscular routes.[11] As a result, the Sabin prototype strains were selected for trial in the United States and in Britain.[12]

When the preparation of oral vaccines was first considered it was thought that one of the chief advantages would be ease of production. It is doubtful whether many people would now agree with this view, for nobody foresaw the troubles that would arise from the presence of, and testing for, adventitious agents in the vaccine. As no inactivating procedure is used, any adventitious agent derived from monkey kidney tissue can multiply as well as poliomyelitis virus. One virus in particular, the vacuolating agent,[13] has given some trouble; it was present in Sabin's original virus seed,[13] but it now appears that vaccine free of it has been produced.

There are four main uses for oral poliovaccine: first, as the recommended procedure for general immunization; secondly, as an additional method of immunization for people who have already received Salk vaccine; thirdly, in special circumstances—for example, for infants—and fourthly, to counteract an epidemic. Oral vaccine has already been used abroad in these four main conditions, and one important lesson has been learnt: the use of it needs exceedingly careful planning. This is partly because it should be given on the widest possible scale in any area in the shortest possible time once the decision to use it has been taken. This is an administrative problem for which Great Britain is not likely at present to be prepared. Other problems may be solved in the series of investigations being carried out by the Medical Research Council with live vaccine kindly supplied by Sabin. For example, is it still best to use monovalent vaccine in a series of doses, monovalent followed by bivalent, or trivalent? Are booster doses needed? The question also arises whether the vaccine should be used to halt an outbreak such as that in East Anglia. It appears that cases have been occurring in the Ipswich area since the end of February, so on general grounds it would seem too late to step in with a live vaccine. But if other outbreaks occur there would seem to be no reason why the vaccine should not be used provided public health authorities feel confident they can go ahead at a moment's notice. What constitutes an outbreak? The first case of paralytic poliomyelitis should serve as an alarm, and the second calls for action. The old adage that more than one case in a parish constitutes an outbreak holds good for poliomyelitis.

It has been decided to use a type of virus in the oral vaccine different from the epidemic strain, so as to avoid any adverse opinion if poliomyelitis develops in vaccinated persons while incubating the disease. That this might happen during the first week after receiving live vaccine is to be expected in view of the incubation period in poliomyelitis, and it is something that should be pointed out by those giving the vaccine. Some cross-immunity exists between types 1 and 2, and type-2 Sabin vaccine has already been used under epidemic conditions in Singapore.[14] The crux of the matter is that emergencies should not arise if the population is well and fully immunized. A study recently reported by J. L. Melnick[15] and his colleagues confirms the effectiveness of Salk vaccine.

DIAGNOSIS OF CROHN'S DISEASE

Since the original description of a non-specific granulomatous inflammation of the terminal ileum by B. B. Crohn and his colleagues[1] in 1932, the disease has emerged as a not uncommon cause of abdominal symptoms at all ages. It appears to affect women more frequently than men,[2 3] and symptoms develop most commonly before adolescence. The frequency of the condition in children has recently been emphasized by a series of 28 patients reported from the Mount Sinai Hospital in whom symptoms had developed between the ages of 7 and 15 years.[4] That it can present puzzles in diagnosis—and even after necropsy—is evident from the Clinicopathological Conference reported from the Postgraduate Medical School this week (p. 1227).

Patients present most commonly with abdominal pain either in the right iliac fossa and simulating appendicitis or more diffusely and colicky in type in the lower abdomen owing to partial intestinal obstruction. Fever and vomiting commonly accompany the pain, and tender inflammatory masses may be palpable. Diarrhoea,

either episodic or continuous, is frequently present, accompanied by loss of weight, anaemia, and low-grade pyrexia. Stools may be bulky and fatty, and occult blood can usually be detected in them. Fistulae may develop externally or to an adjacent viscus. Less commonly acute intestinal obstruction, perforation, or melaena may be the presenting symptoms, while unexplained anaemia, fever, oedema, or vitamin deficiency may lead to the suspicion of some other systemic disease.[5]

The diagnosis is often confirmed radiologically[6] in the early non-stenotic phases by showing thickening and blunting of the mucosal folds, ulceration, and inflammatory polyps in the affected segment, though the classical "string sign" described by J. L. Kantor[7] is only rarely observed, being produced by mucosal oedema and ulceration. In the stenotic phase localized strictures develop, with dilatation of the proximal bowel. Lesions involving several bowel segments are sometimes seen. When the condition attacks the colon, the maximal involvement of the right side, with narrowing of the terminal ileum and formation of multiple strictures, may serve to distinguish the condition from segmental ulcerative colitis, though the distinction may be nearly impossible radiologically.[8 9] Anaemia, moderate leucocytosis, and steatorrhoea may be associated non-specific laboratory findings. A normal chest radiograph and negative Mantoux reaction tend to confirm that the lesion is non-tuberculous, though laparotomy may be necessary to exclude it.

The fact that Crohn's disease could affect the colon as well as, or instead of, the small intestine was first noted by R. Colp in 1934.[10] Since then its relationship to and distinction from segmental ulcerative colitis and other forms of enterocolitis has caused much confusion and has been the subject of several recent papers. M. B. Goldgraber and colleagues[11] believe that these conditions may be some sort of autoimmune disease. H. E. Lockhart-Mummery and B. C. Morson,[8] reporting 25 patients with Crohn's disease of the large intestine, and G. Watkinson and colleagues,[9] reporting 15 patients with supposed segmental colitis, emphasize difficulties of distinction between Crohn's disease, ulcerative colitis, and non-specific enterocolitis[12] on clinical, radiological, and pathological grounds. Distinction can sometimes be made by rectal biopsy, when the demonstration of non-caseating giant-cell systems in the submucosa supports the diagnosis of Crohn-type lesions.[8] Watkinson and others[9] consider that colitis, Crohn's disease, and non-specific enterocolitis differ so strikingly in natural history, in tendency to recurrence after surgery, and in response to medical treatment that it is incumbent on the clinician and pathologist to attempt to distinguish them, so that the most suitable treatment may be advised and an accurate prognosis given.

[1] Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D., *J. Amer. med. Ass.*, 1932, **99**, 1323.
[2] Van Patter, W. N., *et al.*, *Gastroenterology*, 1954, **26**, 347.
[3] Cooke, W. T., *Ann. roy. Coll. Surg. Engl.*, 1955, **16**, 137.
[4] Moseley, J. E., Marshak, R. H., and Wolf, B. S., *Amer. J. Roentgenol.*, 1960, **84**, 532.
[5] Jones, F. A., and Gummer, J. W. P., *Clinical Gastroenterology*, 1960, p. 451, Blackwell Scientific Publications, Oxford.
[6] Marshak, R. H., and Wolf, B. S., *Amer. J. Roentgenol.*, 1955, **74**, 1000.
[7] Kantor, J. L., *J. Amer. med. Ass.*, 1934, **103**, 2016.
[8] Lockhart-Mummery, H., and Morson, B. C., *Gut*, 1960, **1**, 87.
[9] Watkinson, G., Thompson, H., and Goligher, J. C., *Brit. J. Surg.*, 1960, **47**, 337.
[10] Colp, R., *Surg. Clin. N. Amer.*, 1934, **14**, 443.
[11] Goldgraber, M. B., Kirsner, J. B., and Palmer, W. L., *Proceedings of the World Congress of Gastroenterology, Washington*, 1958, Vol. 2, p. 935.
[12] Cooke, W. T., and Brooke, B. N., *Quart. J. Med.*, 1955, **24**, 1.

PREMATURITY

The prevention of prematurity and the care of premature infants are the subjects of a report[1] issued this week by a committee of the Central Health Services Council under the chairmanship of Sir Andrew Claye. Nearly 8% of all notified births in England and Wales in 1959 were premature, and the report estimates that over 5,500 deaths of infants each year are due to prematurity; that nearly 60% of infants who die in their first week of life are premature; and that 54% of 15,403 stillbirths notified in 1959 were premature. The cause of premature labour is unknown in about half the cases, and in the remainder the most important associated conditions are toxaemia, antepartum haemorrhage, and multiple pregnancy.

The rate of survival of premature infants is directly proportional to the birth weight, and the prognosis for infants in the higher weight groups—from 4 lb. 15 oz. (2,250 g.) to 5 lb. 8 oz. (2,500 g.)—is excellent. The facilities available for the care of infants of lower weight varies greatly from one part of the country to another, and the report states that an inquiry carried out in 1956 disclosed that only 45% of premature infants in the lowest weight group—3 lb. 4 oz. (1,500 g.) and under—were admitted to specially equipped and staffed premature baby units.

The report states that there are advantages in combining the care of premature infants in hospital with that of mature ill infants, and recommends that units for this purpose should be attached to large and medium-sized maternity departments. The committee estimated that for every 1,000 live births at home or in hospital at least six cots will be needed for premature infants or ill newborn mature infants. Units should not be of less than twenty cots, and a unit of this size would serve a population of 200,000. The consultant paediatrician in collaboration with the consultant obstetrician and medical officer of health should be responsible for the co-ordination of home and hospital care.

Twenty-two per cent. of all notified premature births took place at home in 1959, and while this figure can be reduced by better selection of cases for hospital confinement the committee recommends that a service for the care of premature babies at home should be provided, and a resuscitation team should be able to go out at any time of the day or night to emergencies in the home or in hospital. Special arrangements for the transport of premature infants will be needed.

The final recommendation in the report is that a perinatal mortality committee—of obstetricians, paediatricians, pathologists, medical officers of health, and senior midwives—should be set up in the area

[1] Ministry of Health, Central Health Services Council, *Report of the Sub-committee on the Prevention of Prematurity and the Care of Premature Infants*, 1961. H.M.S.O., London. Price 9d. net.

served by a special unit of the hospital to review perinatal deaths, to define causes, and to assess avoidability. Similar committees have worked well in the past, and this is one of several practical suggestions made in this useful report.

YOGA AND THE HEART

Some Yogis claim to be able to stop their heart beating for a short period at will. Swami Vivekanand[1] wrote, "There is not a single muscle in the body over which man cannot establish perfect control by practice, even the heart can be made to stop or go on at his (Yogi's) bidding . . . ." Recently B. K. Anand and G. S. Chhina[1] have been able to study three Yogis who volunteered to be examined scientifically during this feat.

The manœuvre by which the Yogis claimed to stop their heart beating was found to be essentially a Valsalva manœuvre. During the act the Yogis were seen to perform powerful forced expiration against a closed glottis for between 10 and 20 seconds, with resultant disappearance of both pulse and heart sounds. Only a faint murmur was audible over the praecordium with a stethoscope, and it was due partly to the forceful contraction of the intercostal muscles. At the same time the neck veins became engorged. By means of simultaneous radiography and electrocardiography the heart was shown in fact to be contracting throughout the period when the pulse and heart sounds had disappeared. During the forced expiration against a closed glottis, the electrocardiogram showed that the heart rate quickened and then, when normal respiration was resumed, it continued slower than normal for some time. With the slowing of the pulse the blood-pressure rose above the normal resting level and the pulse-pressure increased. Since intra-arterial records of blood-pressure were not obtained, there was no measurement of the mean blood-pressure during the act of forced expiration. These circulatory changes parallel closely those seen during and after the Valsalva manœuvre in the healthy subject.[2,3]

SAFETY BELTS IN CARS

Per mile travelled, the occupant of a car has about the same risk of being killed as an airline passenger. His risks of injury are considerably higher. Yet, whereas seat belts are universal on our airlines, they are still rare in our cars, and this despite the fact that the protection they offer is almost certainly more valuable in the relatively low-speed accidents of road vehicles.

The majority of deaths and serious injuries suffered by the occupants of cars in accidents are due to ejection from the vehicle or impact with its interior. Both can be virtually eliminated by a good safety harness. When supported by such a harness, the human body can tolerate surprisingly high decelerations. The heroic experiments of Colonel Stapp in the United States have shown that decelerations of fifty times the force of gravity can be tolerated. This can be compared with the familiar dangers of minor injury in a car when the occupants are thrown forward during severe braking: the force of so-called 100% braking efficiency is 1 *g*. In the absence of a restraining harness the human body continues forward at the same speed, and many experiments have shown that, by the time the head or chest strikes the interior of the vehicle, this is often stationary or actually recoiling backwards. The force of impact is then extremely great, which accounts for the severe head and chest injuries.

In the United States comparisons have been made between accidents in which the occupants of the car were using seat belts and other similar accidents in which they were not. They showed that the wearers of belts avoided about three-fifths of the injuries, and this even with simple lap straps. Such straps, though perhaps adequate in large American cars, are insufficient in smaller European cars, where the clearance for forward movement of the body is very restricted. The most effective seat belt is the complete harness similar to that of an air pilot, but some compromise with acceptability may be necessary. Once in position, a complete harness can be very comfortable, since it provides stabilization against the vibration and jostlings of road travel. Incidentally, it also reminds the driver not to try to reach around the car while driving. Probably the most extensive experience has been in Sweden, where about one-half of the cars are stated to be fitted with belts. Their single diagonal belt is convenient to use, but the protection it gives against ejection leaves something to be desired, and a three-point type of suspension which includes a lap belt has now been introduced.

British requirements are not necessarily the same as in either the United States or Sweden. Our cars and traffic conditions are both different. A good start has been made here with the British Standard for car safety belts (B.S. 3254), which specifies adequate strength of webbing and strength and performance of buckles. There is plenty of scope for various designs within this specification, and it is obviously an advantage to have several different patterns to choose from so that individual preferences can be suited. Some new suggestions on how the belts can be put on with greater ease would be welcome. The manœuvre is rather like that of putting on a waistcoat while sitting down, and involves awkward movements of the shoulders. Next year several motor firms promise standard fittings for belts. Perhaps we must wait longer for the belts to be incorporated in the seats of popular cars, but we can make ourselves appreciably safer with types already on the market.

The Council of the Association has informed the Ministry of Defence that the Ministry's arguments against increasing the pay of National Service medical officers are **entirely unacceptable.** Owing to a printing error, it was stated in last week's *Journal* (p. 1161) that these arguments were acceptable.

[1] Quoted by Anand, B. K., and Chhina, G. S., *Ind. J. med. Res.*, 1961, **49**, 90.
[2] Elisberg, E., Singian, E., Miller, G., and Katz, L. N., *Circulation*, 1953, **7**, 880.
[3] Lee, G. de J., Matthews, M. B., and Sharpey-Schafer, E. P., *Brit. Heart J.*, 1954, **16**, 311.

Clinicopathological Conference

A CASE OF CROHN'S DISEASE

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a young girl with Crohn's disease who was treated in several hospitals and finally died in the West Middlesex Hospital, Isleworth. (Hammersmith Hospital, Case No. 205485; P.M. No. S.60/414.) The guest speaker was Dr. N. F. Coghill, of the West Middlesex Hospital.

Clinical History

Dr. N. F. COGHILL: This girl died aged 18. Her medical history began at the age of 6½ years with measles and pneumonia in 1947. During the next 12 years she spent about three and a half years in hospital or otherwise away from home and underwent five abdominal operations.

Her first admission to hospital was for five months in 1948 because of anorexia, loss of weight, and abdominal pain following the pneumonia. She weighed 17.3 kg. and measured 3 feet (0.9 m.) in height. Her abdomen was distended, there was a hypochromic anaemia (Hb 9.6 g./100 ml.), the E.S.R. was raised, and there was a continuous remittent fever (to 101° F. —38.3° C.). There was neither blood nor excess fat in the stools. Her Mantoux reaction was negative. A barium-meal and follow-through examination was normal. She was discharged in the same state, no definite diagnosis being made.

SECOND ADMISSION

She was admitted to another hospital in May, 1950, at the age of 9, with intestinal obstruction. At laparotomy the surgeon considered the diagnosis was plastic tuberculous peritonitis. Subsequent barium-meal examination indicated partial obstruction in the mid-part of the small intestine. A barium enema revealed a normal colon. Her Mantoux reaction remained negative.

In January, 1952, she was vomiting and losing ground. She weighed 12.7 kg. and 46% of the dried faeces consisted of fat. A barium meal showed dilated coils of small intestine with thickened walls and mucosa, suggesting jejuno-ileitis (Fig. 4). At laparotomy what was thought to be a soft tumour was found blocking the mid small intestine. This was removed, together with a mesenteric lymph node, and an end-to-end anastomosis was made. The "tumour" was found to be intestine narrowed by cellular and fibrotic inflammatory changes. The lymph node contained epithelioid follicles but no caseation.

Because of recurrent intestinal obstruction another laparotomy was done 18 months later. The jejunum was dilated above a thickened area which was kinked and adherent to the transverse colon. Adjacent mesentery was thickened and lymph nodes enlarged. A bypass was constructed round the jejunal obstruction. In December, 1955, at the age of 14, another barium meal showed that a blind loop was developing in the small intestine, probably at the site of the last operation, although understandably this was not clearly recognized at the time. Symptoms of intermittent partial intestinal obstruction continued. Her diet was poor, the protein intake often being no more than 25 g. per day. Diarrhoea appeared. Her weight varied, and she had a hypochromic anaemia (Hb 48%).

FIRST ADMISSION TO HAMMERSMITH HOSPITAL

In October, 1957, at the age of 16, she was admitted, under the care of Professor T. Russell Fraser, in a poor clinical state—apathetic, lethargic, dwarfed, wasted, and with ankle oedema. Her skin was dry and scaly. There was no secondary sex development. Her height was 4 feet 4½ inches (1.33 m.), suggesting an age of about 9½ years, and her weight was 20.9 kg., the weight of an average 6-year-old child.

Investigations

Sigmoidoscopy was normal. *Blood:* Hypochromic anaemia persisted (Hb 11.9 falling to 7.5 g./100 ml.). Serum proteins: total 4.4 g./100 ml.; albumin 1.0 g./100 ml. The serum potassium was 2.1, calcium 4.1, and phosphate 2.0 mEq/litre. Blood urea was 6 mg./100 ml. The prothrombin time was prolonged, suggesting vitamin-K deficiency. The serum vitamin-B_{12} level was 80 $\mu\mu$g./ml. A folic-acid absorption test indicated almost complete inability to absorb this substance.* She was unable to absorb vitamin B_{12} given with intrinsic factor. Fat absorption was impaired (24% of 40 g. intake). *Renal:* The urinary excretion of ketosteroids and ketogenic steroids was only 1–2 mg. per 24 hours.

Radiological: Her bones showed evidence of osteoporosis and the bone age was 12–14 years. A barium meal now showed a stricture in the jejunum. In retrospect, though not appreciated at the time, signs of a blind loop were visible in the lower jejunum. The colon was dilated and lacking in haustrations, and the right half was bunched up under the liver. A barium enema (Fig. 1) showed a stricture in the sigmoid colon and confirmed the presence of general colonic disease; barium would not pass the proximal end of the transverse colon.

Treatment and Subsequent Course

Vigorous treatment with an intragastric drip, electrolyte replacement, gluten-free diet, and cortisone improved her general condition. Tetracycline reduced faecal fat from 14 to 8 g. per day, suggesting that the steatorrhoea was due to stricture or blind loop. Her weight remained almost unchanged.

After discharge on a gluten-free diet, cortisone, and tetracycline, she improved remarkably, and by January, 1958, her weight had reached 27.5 kg. She was well and at work. Her serum proteins were normal. Cortisone was stopped in February. She was readmitted in May for balance studies. Her appearance then is shown in Fig. 2. Sexual development had hardly begun, but she had grown one inch (2.5 cm.) in height and her mental state was improved. The

*Chanarin, I., Anderson, B. B., and Mollin, D. L., *Brit. J. Haemat.*, 1958, 4, 156.

alkaline phosphatase was 29 K.-A. units. The serum vitamin-B_{12} level had risen to 230 $\mu\mu$g./ml. (without treatment). The glucose-tolerance curve was flat. The faecal fat measured 4.8–5.9% of the intake on a gluten-free diet, and 2.8–3.7% when 15 g. gluten was added to her food daily. This suggested that removing gluten from the diet was not a material factor in any recovery which had taken place and that her steatorrhoea was not due to gluten-sensitivity. Because an ileo-colic fistula was suspected another barium meal was done. This now clearly demonstrated a blind loop in the small intestine, but no fistula was discovered.

FIRST ADMISSION TO THE WEST MIDDLESEX HOSPITAL

Her next admission, in January, 1959, was to the West Middlesex Hospital, because it was nearer her home. Abdominal pain and vomiting had occurred and she had begun to lose weight again. At this time her height was 4 ft. 6½ in. (1.38 m.), and her weight 19.1 kg. Her appearance is shown in Fig. 3. There was scanty axillary hair. The blood-pressure was 90/70 mm. Hg; E.S.R. 30. There was a macrocytic anaemia (Hb 10.5 g./100 ml.), the bone marrow showing macro-normoblastic erythropoiesis. The serum calcium was 4.3 mEq/litre. 45.2% of a dose of fat tagged with radio-iodine (I-131) appeared in the stools, but only 5.3 g. of chemical fat was present daily over a six-day period. A barium meal (Fig. 5) appeared to show a dilated duodenum and a poorly outlined small intestine, barium reaching the rectum in three-quarters of an hour.

Prednisolone was given and tetracycline continued. She remained unable to absorb folic acid, but vitamin-B_{12} absorption was now normal when given with intrinsic factor.

TERMINAL ILLNESS

She remained fairly well until September, 1959, when, at the age of 18, she was admitted with haematemesis and melaena. Her blood-pressure fell to 70/30, but she was resuscitated easily. It was assumed that she had an acute peptic ulcer probably as a result of steroid therapy. Her weight was unchanged. The serum calcium fell to 2.6 mEq/litre and she had severe tetany requiring much intravenous calcium gluconate for relief. There was 21.4 g. of fat daily in the stools. Obstructive episodes recurred.

A review of past barium-meal radiographs now made it clear that a duodeno-colic fistula had developed (Fig. 5). Further films have become available since her death, and the whole series may be reviewed at this point. With regard to the fistula the question arises, Did the disease occur in the duodenum first and spread to the colon or vice versa, or were both diseased together? Radiographs in April, 1952, revealed a normal duodenum, but one film (Fig. 6) showed that the right half of the colon was contracted and without haustrations, and its mucosal pattern was abnormal. Radiographs in December, 1955, showed a still-normal duodenum. In April, 1957, as was suspected, barium was beginning to leave the duodenum by a small fistula (Fig. 7). It appears, therefore, that diseased colon became adherent to healthy duodenum and eventually resulted in a fistula and spread of the disease into the duodenum.

At laparotomy, under cortisone cover, the large fistula, the blind loop, and the sigmoid stricture were confirmed. The fistula was undone with removal of

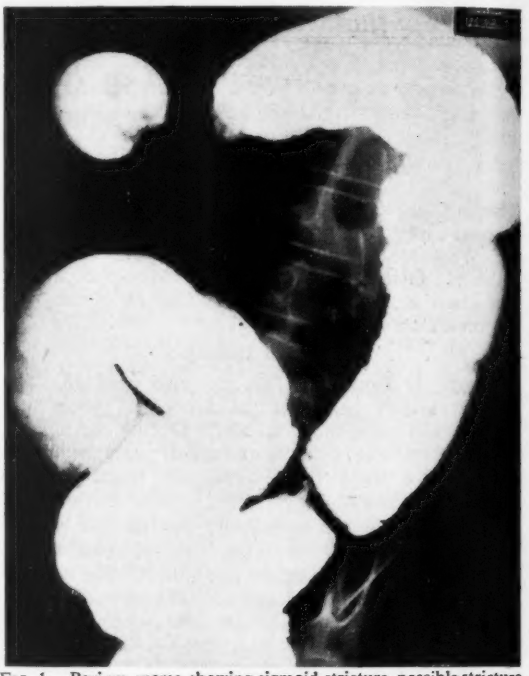

FIG. 1.—Barium enema showing sigmoid stricture, possible stricture in the transverse colon, and generally diseased colon (December, 1957).

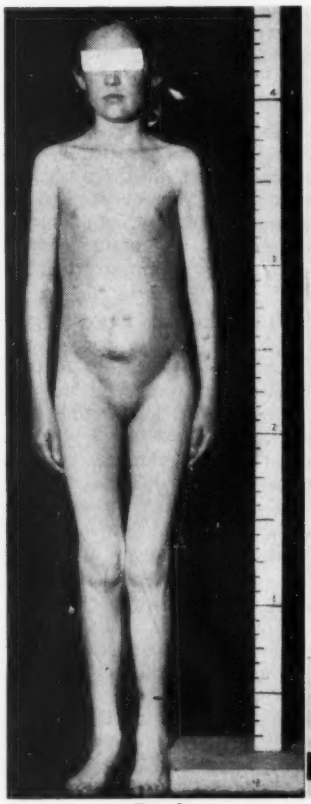

FIG. 2

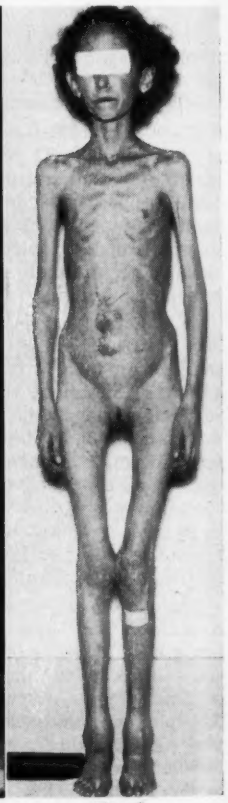

FIG. 3

FIG. 2.—Appearance and nutritional state in May, 1958, aged 17.
FIG. 3.—Appearance and nutritional state in January, 1959, still aged 17.

FIG. 4.—Gas-filled dilated coils of small intestine showing thickened walls (February, 1952).

FIG. 5.—Barium meal showing barium passing from the duodenum into the transverse colon (February, 1959). The arrow shows the fistula.

FIG. 6.—Radiograph after barium meal in April, 1952. The arrow points to the contracted abnormal colon.

FIG. 7.—Radiograph after barium meal in April, 1957. The arrow indicates the first evidence of a duodeno-colic fistula.

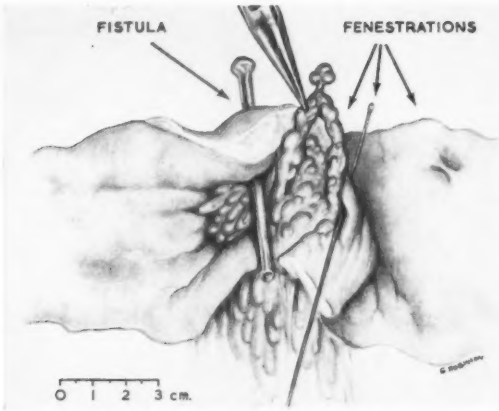

FIG. 8.—Artist's drawing of resected bowel.

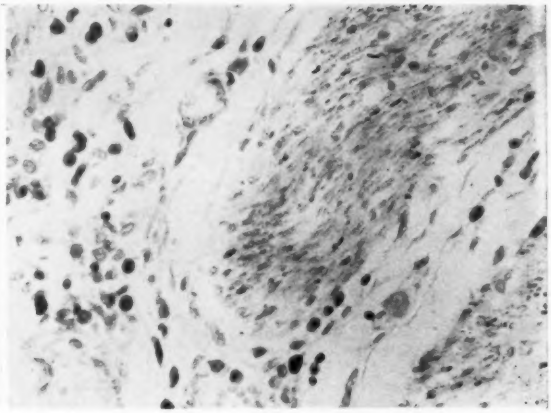

FIG. 9.—Muscularis of ileum showing acid-fast pigment granules in the muscle fibres and an infiltration of the loose connective tissue with plasma cells and mast cells. (×300.)

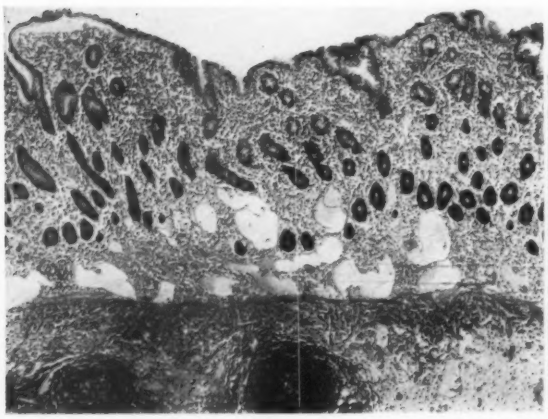

FIG. 10.—Inflamed intact ileum showing local loss of villous pattern, distension of mucosal lymphatics, and submucosal lymph follicle hypertrophy. (×40.)

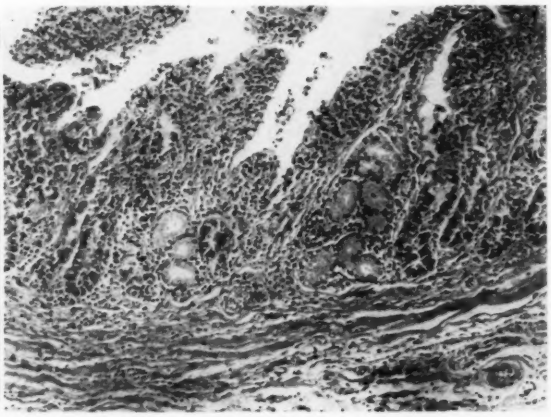

FIG. 11.—Ileal mucosa from the bypassed loop showing mucous cell metaplasia of some of the crypt lining cells. The surface mucosa is missing as a result of post-mortem autolysis. (×70.)

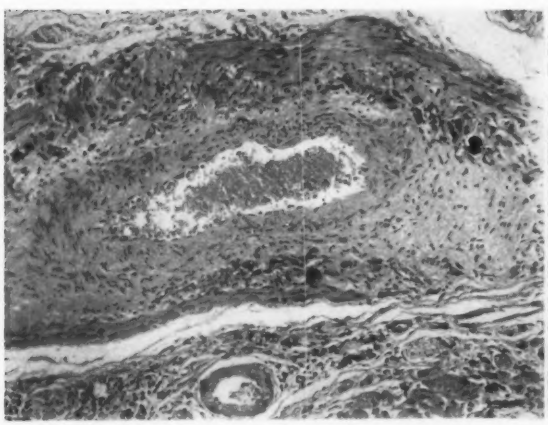

FIG. 12.—Artery in the outer wall of ileo-caecal junction showing fibrous endarteritis and foreign body giant cells in relation to broken internal elastic lamella. (×95.)

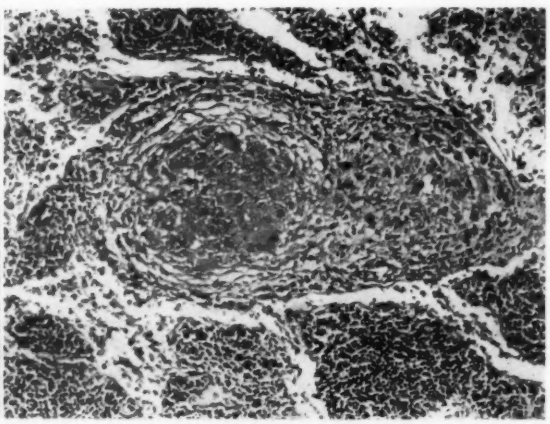

FIG. 13.—Tubercle or sarcoid-like nodules in an oedematous mesenteric lymph node. (×95.)

some diseased duodenum and the right half of the colon. The sigmoid stricture was not causing obstruction. The blind loop consisted of the bypass which had been constructed at the operation in April, 1953, and which had become stretched, and adherent and kinked at its lower end; the obstructed bowel it was designed to relieve had become patent. The lower end of the bypass was freed to abolish the blind loop. The resected colon consisted of a bunched-up mass of bowel with polypoid, fenestrated mucosa (Fig. 8). After the operation she rapidly developed a duodenal fistula with profuse discharge. Profound shock developed and she died six days later.

Clinical Diagnosis

(1) Crohn's disease of the small intestine and colon leading firstly to:

(2) Local lesions causing obstruction, and to

(3) Chronic malabsorption causing severe malnutrition and retarded growth; and finally to

(4) Fistula formation between colon and duodenum which aggravated the malabsorption.

(5) ? Part played by steroid therapy in post-operative breakdown of gut.

Post-mortem Findings

Dr. I. DONIACH: Post-mortem examination was done at the West Middlesex Hospital by Dr. A. Knudsen.

There was a right-sided, subdiaphragmatic collection of purulent fluid arising from a leak from the duodenum at the site of the resected duodeno-colic fistula, and a walled-off collection of purulent fluid resulting from breakdown of the suture line at the site of anastomosis between ileum and transverse colon. The *small intestine* was deformed by a blind loop caused by the previous side-to-side anastomosis. The bypassed loop was 25 cm. long; the rest of the small intestine was 80 cm. long. The mucosa of the small intestine showed scattered areas of oedema and small foci of ulceration. The mesentery was focally thickened and fibrous and had produced a sharp angulation in the blind loop which had reduced the lumen locally. The *oesophagus* and *stomach* were normal. The *colon* was 52 cm. long and presented a fibrous stricture due to an ulcer at the upper end of the sigmoid. The *liver* (1,200 g.) was enlarged, congested, and finely fatty.

The *heart* (170 g.), *kidneys* (120 g. each), *spleen* (125 g.), *thyroid*, and *adrenals* appeared normal both macroscopically and microscopically. The *uterus* and *ovaries* were infantile. The *lungs* (right 215 g., left 235 g.) showed patchy bronchopneumonia.

Histology of the small and large intestine and mesenteric lymph nodes: In addition to post-mortem sections, material was available from the specimen of small and large gut resected six days before death. The diseased bowel, both "surgical" and post-mortem, showed areas of ileum (Figs. 10 and 11) in which the mucosal and submucosal lymphatics were grossly dilated and the submucosa swollen by interstitial oedema and by collections of hypertrophied lymphoid tissue showing lymph-follicle formation. Elsewhere foci of submucosa and subserosa were thickened by fibrous tissue. The ulcers showed replacement of mucosa by necrotic debris lying upon granulation tissue infiltrated with plasma cells and eosinophils. The underlying muscularis mucosae was broken up and hypertrophied. The muscle fibres of the muscularis contained numerous acid-fast lipofuscin pigment granules (Fig. 9). In places the inner muscularis was partly fibrosed. The myenteric plexuses were oedematous. The mesentery attached to diseased areas of small intestine was thickened by fibrous tissue; its arteries showed intimal fibrous endarteritis and a broken internal elastic lamina (Fig. 12). The mesenteric lymph nodes were enlarged by distension of lymphatic sinusoids. One lymph node contained a few non-caseating tubercles made up of mononucleated and multinucleated epithelioid cells (Fig. 13). Between the diseased areas the mucosa of the small intestine appeared normal. An acute ulcer was present in the surgical specimen of duodenum. The resected colon, in the region of bunched-up caecum, showed similar cicatrizing inflammation to that seen in the small intestine together with pseudopolyp formation. The ulcer in the sigmoid colon resembled those seen in the ileum.

Pathologist's Diagnosis

(1) Regional enteritis.

(2) Infantilism due to malnutrition.

Discussion

Dr. COGHILL: Now that we find this disease in other parts of the intestines it has been suggested that it is better to stick to the eponym and call it Crohn's disease rather than regional ileitis or regional enteritis. This is a small point, but the condition is being found increasingly in the colon and it can affect other parts of the alimentary tract.

The question of protein loss is of some interest. No specific tests were done for this here. In fact, techniques for investigating loss of protein into the intestine are only just becoming available. These patients do suffer from hypoproteinaemia and it is possibly not all due to inadequate absorption. There may be a considerable loss of protein from the gut, and recent studies† using substances which are excreted into the gut and not reabsorbed, such as radio-iodinated polyvinyl-pyrrolidone, have shown that there may be considerable loss from the gut in some cases of enteropathy. It is a side of things that might well be explained by the histology which we have seen. The anaemia in these people is commonly iron-deficient, at least in part, and again there must be quite a loss of blood from the gut, though I don't think this particular aspect has been much investigated in this type of case.

STEROIDS AND OPERATION

The rapid, downhill post-operative course interested us. It is, of course, always dangerous to operate on the duodenum, and even when the outlook is much more favourable disaster can occur. But it wasn't only the duodenal sutures which broke down, the colonic sutures also broke down, and the question arises about the part that steroid therapy played here. After colectomies for ulcerative colitis, done under cortisone cover, we have found that, if the steroid is continued for more than seven days, healing of the ileostomy is seriously impaired in some cases. I suggest this may have been a factor contributing to her post-operative course.

Professor J. MCMICHAEL: What would you do now? Would you tail off cortisone before an inevitable operation, or give A.C.T.H.?

Dr. COGHILL: I wonder whether one should give a patient who is likely to require small-gut resection steroids at all.

†Gordon, R. S., *Lancet*, 1959, **1**, 325.

Professor MCMICHAEL: We usually start with some gentler medical measures before we rush to surgery, and you may find yourself compelled to consider colectomy in a patient who has had steroid treatment for ulcerative colitis. Do you feel that, once they have had steroids, you have burned your boats so far as operation is concerned?

Dr. COGHILL: Well, I didn't mean that. I think where ulcerative colitis is concerned and operation is on the large bowel it doesn't matter so much, although I believe that if possible one shouldn't continue steroid cover at the time of colectomy for more than about five days; I think one has got to cut it down quickly. But where the small gut, particularly the upper small gut, is likely to be operated upon at some time, I think one must consider whether it is right ever to give the patient steroids. Obviously each case has got to be taken on its merits. But the dangers of operating on the duodenum are so great anyway, I wonder whether such treatment isn't greatly increasing the risk of a duodenal fistula.

Dr. C. C. BOOTH: I am unsure about the question of this patient's steroids. We have seen patients with Crohn's disease who have been on steroids for between two and three years and have been safely operated on under steroid cover, have healed up, and have done well. We have also seen patients with gross hypoalbuminaemia who have done badly. I can't help feeling that this may be related rather to her protein deficiency and hypoalbuminaemia than to her steroids.

INTRAVENOUS FEEDING

Professor T. RUSSELL FRASER: If I might comment on that, I think it is of interest to go back to when she first came to Hammersmith Hospital. In January, 1958, she was given roughly the same dosage of cortisone, which I think was about 75 mg. per day, along with her other treatment. It was followed by a striking improvement in her nutrition and everything else. I think, when we talk of the risks of cortisone and its allies, we have to realize that this risk of poor healing is very much a matter of protein metabolism. Fortunately, on this first occasion she didn't have, I suppose, the severe duodenocolic fistula which was a big factor in her final malnutrition. I am reminded of a similarly wasted patient who was once under our care because his gastrectomy had been followed by an anastomosis to the ileum instead of the jejunum. He was a similar operative problem, not because of any steroids (he never had them), but simply from sheer inability to absorb food. I wonder whether the real answer to this sort of patient wouldn't really be intravenous feeding for a fortnight before operation, rather more than any question of steroids or not steroids. It is possible that the steroid dosage was a little bit on the high side, but I think the fact that food was not being absorbed must have been very important.

Dr. COGHILL: Yes, I quite agree. Obviously protein malnutrition must be a big factor in a case like this. Earlier diagnosis of the fistula might have helped in this case. It is obvious that everybody who handled this patient missed one or two things about her; we certainly did badly at the end, and, if it had been possible perhaps to deal with the colon before it got stuck on to the duodenum and ulcerated to form a fistula, her state might have been different. But it is very easy, looking back in a case like this, to think of things one ought to have done.

GLUTEN AND ANTIBIOTICS

Professor RUSSELL FRASER: Yes, when she first came our way she was so terrifically undernourished (much worse than the appearance in Fig. 3) that operation was in our view entirely out of the question, and as you see she was put on blunderbuss therapy, based on the probable diagnosis of both a blind loop and Crohn's disease. And, as she seemed to be doing so well on that, we waited from month to month wondering which day it would be safe to operate, and, as you will have noticed, withdrew the various aspects of treatment trying to find which one of them mattered. The gluten-free diet seemed to be ruled out as unimportant; the tetracycline we felt was obviously important, but what we didn't know was whether the cortisone was contributing, and that was why it was withdrawn in February, 1958. We concluded, evidently unwisely, because she showed no change for the worse over the next five or six months, that it wasn't essential. Perhaps we should not have expected her Crohn's disease to relapse quite so quickly.

Dr. M. MILNE: Surely the usual rule in these controversies is that the two together are important rather than either one or the other. I remember a child recently operated on for thrombocytopenic purpura who developed a gastric fistula which fortunately cleared. Now the surgeons were strongly of the opinion that this was purely a cortisone effect from the previous treatment for the thrombocytopenic purpura. Certainly there was no protein malnutrition here; she was a very healthy girl except for her purpura, and took enormous amounts of protein on the ward. So I think it is a mixture of both and not either one or the other exclusively.

POTASSIUM DEFICIENCY

I should like to ask Dr. Doniach whether there were any lesions of potassium deficiency in this patient. The patient with a gastro-ileal fistula whom Professor Fraser mentioned had severe necrosis in the myocardium and typical renal lesions. We didn't see those interesting organs.

Dr. DONIACH: We did receive sections of the heart and kidney from the West Middlesex and I didn't see those lesions, but I'll confess I didn't look for them. I had better have another look, but I can say they weren't outstanding.

Just one other point, since Dr. Coghill has brought up the question of the naming of this disease; I was amused to read that Dr. Crohn first suggested calling it "terminal ileitis," but his audience thought this would be rather a depressing name, so he changed it to "regional ileitis." Doesn't enteritis include the large gut, or am I being unclassical?

Dr. COGHILL: What about the stomach and oesophagus, where it has also been described?

Dr. DONIACH: Yes, I see.

I wonder if you could explain the flat glucose-tolerance curve in this case.

EXTENSIVE MALABSORPTION

Dr. BOOTH: I think it is worth emphasizing that this is an unusual case of Crohn's disease. Crohn's disease usually involves the terminal ileum. That is as Crohn originally described it. But within a year of his original description it had been described occurring primarily

in the jejunum without any involvement of the terminal ileum. That is a rare type of involvement, but it looks as if this patient's disease did in fact start in the jejunum and she may later have developed lesions further down. This, I think, would explain the extensive malabsorption which she had.

Her abnormal glucose-tolerance test and subnormal folic-acid absorption are in keeping with a lesion of the proximal intestine, for these substances are absorbed in the upper small bowel. She had steatorrhoea and a subnormal B_{12}-absorption, indicating that practically the whole of her small intestine was not functioning properly. This is different from the sort of malabsorption we usually see in regional ileitis. If there is Crohn's disease involving the terminal ileum, there is firstly malabsorption of B_{12} without malabsorption of other substances, for vitamin B_{12} is absorbed in the ileum in man. As the disease gets more proximal, or as other factors come in, then there may be steatorrhoea, but absorption of glucose and folic acid may remain normal. Such patients may develop either iron deficiency from blood loss, or a megaloblastic anaemia due to B_{12}-deficiency. Then there is the most extensive type of malabsorption, which this appears to be, where the whole of the gut is involved, and the absorption of substances which are usually absorbed proximally is affected. This would explain the very intense degree of malnutrition that this patient showed throughout her life. As for Dr. Coghill's suggestion of loss of protein from the gut, this has been demonstrated in a number of patients and may well have contributed. The type of deficiency in this patient can be compared with the type of thing that you see in a patient with a very extensive intestinal resection. We have seen recently a patient who showed this same pattern of malabsorption following a resection of all the small intestine, but for the proximal 8 inches (20 cm.) of jejunum. As in this case, there was a progressive decline, gross malnutrition, and finally death.

GROWTH RETARDATION

Professor MCMICHAEL: Would you like to say a word about the secondary endocrine and growth disturbances in your case, Professor Fraser?

Professor RUSSELL FRASER: I think it is a matter of interest and worthy of emphasis that steatorrhoea does quite often present as an abnormality of growth, apparently an endocrine defect, or sometimes just a failure of puberty to appear, sometimes with dwarfing as well. And it is one of the diagnostic snags that we have to bear in mind always when a patient presents with these defects in growth. It isn't of course difficult to understand that a disease or a disorder leading to malnutrition is likely to delay growth, but it is a factor often overlooked because of the absence of diarrhoea or bowel symptoms, and it sometimes exists.

LIVER DAMAGE

Dr. BOOTH: Another observation of interest here, Dr. Doniach, was the liver. In other patients we have seen with gross protein deficiency associated with the malabsorption syndrome due to resection or Crohn's disease (or in one patient with idiopathic steatorrhoea who had gross hypoalbuminaemia and ascites) there has been gross fatty-infiltration of the liver. In this case the changes looked rather mild.

Dr. DONIACH: Yes, but almost every cell had droplets in it. The droplets were small, so they don't stand out so much as big ones. I suppose she had less fat to mobilize.

Professor MCMICHAEL: We had a very interesting experience, and a rather chastening one, early on in the war. A man, who was a bus driver, had had a gastro-enterostomy performed away back about 1923. The surgeon had anastomosed his stomach to his lower ileum, but he still had enough food passing *per vias naturales*, as it were, to maintain his nutrition until he was put on to a very low protein intake at the time of meat rationing. As a result he developed a severe hypoproteinaemia and oedema. We were slow to tumble to the significance of this operation because of 17 years of relative health after it. He was treated for some time with protein infusions—concentrated serum infusions, in fact—as a result of which he developed severe serum jaundice. From this he made a perfectly good recovery on a minimal protein intake. As a result the theory of nutritional factors producing liver cirrhosis, even with the addition of a virus hepatitis, to my mind, was swept out of existence.

Dr. BOOTH: I think that's all right for a protein deficiency, for I don't think anybody would claim that pure protein deficiency, as occurs in kwashiorkor, would ever lead to anything further than fatty change, but we now have two patients with proved idiopathic steatorrhoea who have histologically proved hepatic cirrhosis.

Professor MCMICHAEL: What is the denominator of your equation; how many didn't have cirrhosis?

Dr. BOOTH: I think that so far there are about 15 who haven't had cirrhosis. There was a discussion at the Royal College of Physicians about this last year at which Dr. Coghill suggested that there was in fact an increased incidence of cirrhosis in idiopathic steatorrhoea, but Dr. W. T. Cooke, from Birmingham, said that he had seen 25 cases at post-mortem, only one of which had hepatic fibrosis. We have recently seen a patient presenting at the age of 67 with idiopathic steatorrhoea who had hepatitis at the age of 21, and he now has a frank cirrhosis.

Professor MCMICHAEL: We had one patient, about 17 years ago, who had severe steatorrhoea and colitis and he developed jaundice, but it was a sort of cholestatic type of jaundice—rather like the type of thing you get with chlorpromazine. I quite agree that the liver may be affected. There is fatty change and there may be other interferences with liver function which indicate this, but I would have thought that cirrhosis is largely an accidental accompaniment.

RADIOLOGICAL DIAGNOSIS

Dr. J. LAWS: I think a word should be said about the *x*-ray changes in this case. The patient was examined many times, and this is often the fate of patients with rather complicated small-bowel lesions. In particular, I think it illustrates the difficulty of demonstrating and appreciating a fistula between the small and large bowel. Commonly the pressure in the large bowel is higher than in the small bowel, so that the contents pass more easily from the colon into the small bowel than vice versa. On a conventional follow-through examination one often finds that only a very small quantity of barium will short-circuit, so that it is uncommon to show a fistula clearly by a follow-through examination unless

it is a very big one. In this case I think it probably was quite a large one and I think that it probably was missed. The fact that the barium entered the rectum in three-quarters of an hour should make you suspect a short-circuit unless the patient has had a resection. This patient had not had such a big resection of terminal ileum or distal small bowel as to account for this degree of hurry.

The examination of choice in these cases is of course a barium enema, but if the large bowel is involved, as it was in this case, and the barium can't be made to flow right round the colon into the caecum, you may be in great difficulty in demonstrating the fistula in this way also. Occasionally it is worth while intubating these patients, but I don't think it would have helped in this particular case. In the case of the gastro-ileostomy which Professor Fraser mentioned, it was intubation which solved the problem in the end and demonstrated the short-circuit between the stomach and the ileum. So in a really difficult case where this kind of fistula is suspected, I think small-bowel intubation is worth considering.

Dr. COGHILL: Yes, we did restrict investigations during her last year of life. She was very ill and we estimated that she had had 15 barium-meal and follow-through examinations, two barium enemas, and numerous chest and bone *x*-rays. Obviously we were practising what I believe the Americans call "diagnostic reticence." We could have done another barium enema because I am sure that terminally it would have shown up this fistula well.

The question of jaundice: I think it is an interesting subject. One or two of our steatorrhoea patients have died with mild jaundice. There is usually little to be found in the liver. I remember your case, Professor McMichael, very well. He is the only example that I can think of which fits the "Birmingham" disease of ileo-colitis. Of course, this girl suffered from ileo-colitis in the sense that she had her ileum and colon involved in an inflammatory process and she had steatorrhoea, but I don't think she could be considered to be a case of ileo-colitis as defined by Cooke and Brooke in 1955.‡

VITAMIN B_{12}

There is one other point about the absorption of vitamin B_{12}. Would you agree, Dr. Booth, that the fact that her B_{12}-absorption improved and that her serum level came up without treatment suggested that her main difficulty in absorbing B_{12} was due to the blind loop, in that absorption improved with antibiotics?

Dr. BOOTH: Yes, I think that so far as absorption is concerned that is so. I am a little dubious about the serum level going up as far as that without treatment.

Dr. COGHILL: At least it suggests improvement. It is a little odd because her terminal ileum was in fact disordered.

Dr. BOOTH: What puzzles me even more is the fact that in her terminal illness she had a normal absorption of B_{12} which would suggest that her distal small intestine was functioning normally. Yet a substance like folic acid was not absorbed. Dr. Mollin and I have seen a patient who has had eight inches (20 cm.) of his proximal intestine resected. He has enough distal intestine to absorb both fat and B_{12} normally, and he also absorbs folic acid. We concluded that folic acid can probably be absorbed indiscriminately from any part of the small gut. One just wonders whether, if the folic acid was given in a fluid dose, it went straight through into the colon, whereas the dietary folic acid may have been absorbed a little better. This might account for the lack of evidence of folic-acid deficiency in this case.

‡Cooke, W. T., and Brooke, B. N., *Quart. J. Med.*, 1955, **24**, 1.
§Broberger, O., and Perlmann, P., *J. exp. Med.*, 1959, **110**, 657.

WHAT IS CROHN'S DISEASE?

Professor MCMICHAEL: I have one further question to put to Dr. Doniach. We have been talking all round this subject, but we haven't really come to the heart of the matter. What is the nature of the disease from which this girl died? What is Crohn's disease? Is it related to sarcoidosis or not?

Dr. DONIACH: I think the idea of its relation to sarcoidosis is dismissed by most people now. The cause of the inflammation has had a number of aetiologies ascribed to it: bacterial, viral, or sensitization. I don't think there has been really any strict advance on that. The latest view is that it may be an auto-immunization, but that again has had no proof. In fact, the only possible intestinal disease in which there has been some evidence is ulcerative colitis. Recently there have been demonstrated§ precipitins in the blood of patients with ulcerative colitis, precipitins towards foetal or infantile colon.

Dr. COGHILL: You are referring to the Swedish work. No one has published any work on auto-antibodies in Crohn's disease yet. The question arises as to how many cases of ulcerative colitis are really examples of Crohn's disease. It is said that sarcoidosis never turns up in people with Crohn's disease, and I have never seen a case, but we have had a curious experience recently: A patient with extensive Crohn's disease of the colon had her colon removed and the wounds all broke down. The abdominal wound ulcerated and at biopsy showed a remarkable picture of sarcoid-like reaction underneath and involving the skin; an appearance which my colleague, Dr. Knudsen, has seen previously in Crohn's disease of the small intestine.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

Radioactive Materials in Food and Agriculture contains a summary of the conclusions and recommendations of an Expert Committee of F.A.O. on Radioactive Materials in Food and Agriculture. More detailed information and conclusions are to be found in five technical appendices. The Committee was set up in response to a recommendation of the Tenth Section of the European Commission on Agriculture and to a resolution of the United Nations Scientific Committee on the Effects of Atomic Radiation: (1) to review present knowledge of the behaviour of radioactive substances in terrestrial and aquatic food chains, including their levels in foods and agricultural materials, and practices which affect the radioactive contamination of human diets; (2) to indicate possible improvements in surveys of radioactive substances in foods and agricultural materials; and (3) to make recommendations regarding research on food chains needed to further the understanding and reduction of the radioactive contamination of the diet of man. (F.A.O. Atomic Energy Series No. 2, H.M.S.O., price 7s. 6d.)

B.M.A. ANNUAL CLINICAL MEETING

CANTERBURY, APRIL 13-16

We reported last week (April 22, pp. 1162–7) the opening proceedings, the session on the relationship between patient, practitioner, and consultant, and the three-part symposium entitled "Looking Ahead in Medicine." This week we conclude our report.

SCIENTIFIC PROCEEDINGS

Friday, April 14

SYMPOSIUM ON PYELONEPHRITIS

A symposium on "Pyelonephritis in Adults and Children" was held in the Parry Hall after lunch, with Dr. T. S. RODGERS (Canterbury) in the chair.

Dr. J. F. SMITH (London) said that as a student one learnt that pyelonephritis was a suppurative inflammation involving the pelvis and parenchyma of the kidney and due to proliferation of bacteria at those sites. He would like this simple concept to continue. There was not much disagreement about the acute form, which was florid at necropsy and often associated with some form of obstruction of the lower urinary tract. Kass* and his associates in the U.S.A. had emphasized the importance of bacterial counts in fresh urine, a count of more than 100,000/ml. being significant, and had shown that in pregnant women attending the Boston City Hospital 5% had counts exceeding this number. These were the ones who, if untreated, proceeded to develop pyelonephritis of pregnancy, but if treated did not. It therefore seemed that by careful examination of the urine pyelonephritis of pregnancy could be prevented. The value of this work was perhaps to stress the importance of the number of bacteria in the urine, although there might be dispute on how this should be assessed.

The chronic form of the disease was a sequel to the acute, and the histological picture was not diagnostic, the diagnosis being made from the surgical or post-mortem specimens. Hodson's work on the radiological appearances,† which were due to surface scarring and clubbing of calices, had been borne out by his own observations at necropsy. The focal scarring differed from ischaemic scarring in that there was no caliceal distortion in the latter. There were almost certainly cases where the changes were minimal with no obvious deformity of the calices and therefore no radiological changes. Nevertheless, radiological investigation was a good working line. The vast majority of cases of chronic pyelonephritis seen by the pathologist showed focal scars. Those occasional examples where the end-result was a diffusely contracted kidney should be regarded critically and a search made for underlying factors such as toxic damage to tubules by drugs and hypokalaemia.

Obstruction was probably the most important pathogenic factor and its cause might be anatomical, functional, or unknown. Often no dilatation of the pelvis or ureter could be found. The picture was one of obstruction with subsequent bacterial infection.

Diagnostic Difficulties

Professor H. E. DE WARDENER (London) said that pyelonephritis was the commonest renal disease and the most difficult to diagnose. A series of 15 treated cases were subsequently surveyed to assess as far as possible the relation of the diagnostic procedures to each other, the effect of treatment, and the extent of the damage sustained. Four renal biopsies showed acute inflammatory necrosis in the cortex, but two of these cases also yielded negative biopsies, these being obtained within minutes of the positive ones. This was due to the focal distribution of the disease. It was stressed that these were obtained from patients who had had what would normally be called "pyelitis." It was, therefore, not unlikely that any patient with pyelitis had these necrotic areas. In one case only (not one of four mentioned) did the intravenous pyelogram show a distorted calix. This turned out to be due to pyelonephritis, but the appearance had suggested a neoplasm and this was why nephrectomy had been performed. Proteinuria, bacteria in the urine, and the W.B.C. excretion rate were inconstant. He concluded that acute pyelonephritis was a disease that probably in all cases caused necrosis in part of the cortex, that it was not necessarily associated with changes in the intravenous pyelogram or with proteinuria, that in most cases it could occur without any demonstrable obstruction of the urinary tract, and that its treatment was not as easy as one might think.

For chronic pyelonephritis it was difficult to define a group to study, but a group had been investigated having the criteria of a positive biopsy and abnormal intravenous pyelograms with a recurrent history of upper urinary infection. The conclusions were that there need not be a history of recurrent upper urinary infection, that there was a stage in chronic pyelonephritis before changes in the intravenous pyelogram were evident, and that this was the ideal time to diagnose the condition. How to do this was a problem, but the first step to improve our methods was to ascertain white-cell excretion rates and bacterial counts in fresh urine. They did not necessarily correspond and were not diagnostic, but provided valuable supporting evidence. They were tedious tests, but laboratories should be encouraged to perform them. Renal biopsies were diagnostic when positive, but unreliable because of the focal nature of the disease and the technical difficulty of the procedure.

The Wine and Cheese Party, given by the East Kent Division of the B.M.A., at the Frank Hooker School.

*Quinn, E. L., and Kass, E. H. (editors), *The Biology of Pyelonephritis*, 1960. Churchill, London.

†Hodson, C. J., in *Recent Advances in Renal Disease*, 1960. Edited by M. D. Milne. Pitman, London.

Recurrent Infection

Mr. D. INNES WILLIAMS (London) said that it was clear they were not speaking as one team on diagnosis and treatment. The case material of the pathologist, physician, and surgeon was different; acceptance of criteria and interpretation of findings varied. The pathologist and the surgeon saw cases later than the physician. The surgeon saw mainly cases of recurrent infection, some of which went on to chronic pyelonephritis. The disease was bilateral and there was rarely cause for nephrectomy. Where nephrectomy was performed for hypertension, one side being mainly affected, the results were disappointing, unlike nephrectomy for a small kidney due to renal artery stenosis. We must try to diagnose the condition early before "the point of removal" was reached. His contribution was to be the treatment of recurrent infection. This was a common problem at all ages. In the male, some form of obstruction was usually found, but in the female it was more complicated, the urinary tract often being apparently normal. A genital origin might be suspected in adults, but in young girls a careful search was necessary. Some kidney substance was lost at each attack of acute infection, and years could elapse between attacks. It was unwise to be too easily reassured by the spontaneous cessation of attacks during childhood: the time lag between the acute disease and the renal failure which resulted was often considerable, and a disease which was seemingly controlled in childhood might be responsible for death in later life.

Probably the best way to find those cases which were developing chronic nephritis was by intravenous pyelography. Established pyelonephritis with scarred and atrophic kidneys was incurable and ultimately fatal. Single attacks could be cut short by chemotherapy, and sometimes the whole process could be stopped by long-continued chemotherapy. Unfortunately this was unsuccessful in a large number of cases, but the anomaly of the urinary tract which was responsible for the recurrent infection could often be corrected before too much damage was done. The difficult cases were those in which there was no obvious distension of the urinary tract. This occurred mostly in girls, and careful investigation showed an anomaly in a large proportion. Such cases were often associated with minor degrees of bladder-neck obstruction and vesico-ureteric reflux. Operations which widened the neck of the bladder and restored the valvular action of the uretero-vesical junction resulted in a cessation of the attacks of infection if performed before the pyelonephritis process was too far advanced. A cine-film was shown demonstrating vesico-ureteric reflux and the result of surgical treatment.

At the Clinicopathological Conference. From left to right, Dr. G. B. Forbes, Dr. Alan Barker, and Professor John McMichael.

TREATMENT OF THYROTOXICOSIS

On Friday afternoon in the Parry Hall a symposium on the treatment of thyrotoxicosis was held, with Mr. M. R. WILLIAMS (Canterbury) in the chair. Mr. JOHN PULLAN (London) outlined the indications and advantages of surgical treatment of thyrotoxicosis. He emphasized that with adequate pre-operative treatment the mortality for thyroidectomy was extremely low, and that the patient was returned to a normal life more rapidly after surgical treatment than by any other type of therapy. Recurrence of thyrotoxicosis after surgery was a negligible risk, although it could occur at any time up to ten years after operation. In selecting patients for operation the severity of toxicity, the character of the goitre, the age of the patient, and failure of medical treatment should all be considered. The severely toxic patient could best be treated with pre-operative anti-thyroid drugs followed by thyroidectomy. Mr. Pullan thought that the glands causing pressure-symptoms or having an intrathoracic extension should always be treated surgically. He emphasized that nodular goitres did not respond well to radioactive iodine, and the possibility of existing malignant changes in a nodule made surgery the method of choice in these cases. Nodules should be treated on their own merits often, ignoring the toxicity. Radioactive iodine was held to be contraindicated in all patients under 45 because of the fear of the later development of malignancy. Thyroidectomy in young children should be avoided wherever possible owing to the hazards of the operative procedure, and anti-thyroid drugs should be used to tide the patient over until puberty. Contraindications to surgery were previous operations on the thyroid gland in cases for which other forms of treatment were now available and the presence of heart disease or other chronic conditions which increased the morbidity of the operation. In dealing with myxoedema after thyroidectomy Mr. Pullan stressed that its incidence was less in most centres than that produced by the use of radioactive iodine.

Drug Treatment

Dr. RAYMOND GREENE (London), who discussed the drug treatment of thyrotoxicosis, agreed with Mr. Pullan in all he had said about the indications for thyroidectomy. He expressed the disappointment that many physicians had felt in past years at the failure of the anti-thyroid drugs to replace surgery as the primary form of treatment for this disease, but the pre-operative use of these drugs had reduced considerably the post-operative morbidity and mortality of thyroidectomy. It was now possible to prepare most patients for operation as out-patients. The indication for the definitive use of anti-thyroid drugs in the place of surgical treatment was twofold: in the first instance where adequate surgical treatment or radioiodine therapy was not available or the patient refused these forms of treatment, and secondly in the young female patient with a small goitre and a mild thyrotoxicosis who could be adequately controlled by prolonged treatment with drugs. If, however, a relapse occurred, then thyroidectomy was always indicated.

The use of anti-thyroid drugs before the administration of radioactive iodine was, in Dr. Greene's experience, of no benefit in most cases. The anti-thyroid drugs he advocated in treatment were carbimazole and potassium perchlorate. None, however, was free from risk, as they occasionally induced dangerous changes in the blood; and their effect if continued for a long period was rarely permanent.

Dosage of the drug should be gauged by the general response of the patient. An increase in the size of the gland indicated overdosage.

Radioactive Iodine

Dr. E. E. POCHIN (London) discussed the use of radioactive iodine in the treatment of thyrotoxicosis. He agreed with the previous speakers that no patient under the age of 45 should be considered for treatment with it because of the risk of producing malignant damage. The dangers, however, might well prove to be of little consequence. Radioactive iodine had been used for nearly 20 years, and there was no definite evidence that it had produced any increase in malignant change in treated glands, but a longer period of time would have to elapse before this impression could be proved. There was no evidence that the relatively low general body dosage had produced any increase in leukaemia in treated patients. He did not advocate the use of this form of therapy in pregnancy, in the presence of large goitres, or in glands with single nodules. There was a positive indication for the use of radioactive iodine in the treatment of all patients with recurrent thyrotoxicosis following thyroidectomy and in those who had developed sensitivity to anti-thyroid drugs. In patients who were bad operative risks this was the therapy of choice, particularly in patients suffering from heart disease. He agreed with Mr. Pullan that the incidence of myxoedema was high, but after this form of treatment the recurrence of thyrotoxicosis was very common. The exact dosage to be given to any patiept was difficult to estimate by any method, but he suggested that a test dose of radioactive iodine should be given before treatment and the dosage estimated on the uptake and turnover of the radioactive iodine. It was, however, important to stop any anti-thyroid drug for a period before giving the tracer dose. The preparation of the patient with anti-thyroid drugs was not necessary except in very severely toxic patients. One advantage of this form of therapy was that there were no immediate disturbing effects following treatment, but the full effect sometimes was not seen for as long as three months after the administration of the radioactive iodine. He concluded that radioactive therapy shared with every other treatment of thyrotoxicosis the demerit of merely preventing the effects rather than dealing with the cause of thyroid overactivity.

PANEL DISCUSSION ON TRANQUILLIZERS

The chairman, Dr. R. HIERONS (Canterbury), introducing the discussion, pointed out that the introduction of tranquillizing and anti-depressive drugs was one of the most important recent advances in medicine. It presented special problems for G.P.s, as psychiatrists could deal with only a small proportion of patients likely to benefit from these substances.

Dr. D. STAFFORD-CLARK (London) found it useful to divide these drugs into the following groups: (1) Substances derived from chlorpromazine—the phenothiazine drugs. They acted mainly by calming, by reducing tension, anguish, and pain. In general practice chlorpromazine was used in the dosage of 25 mg. three times a day, but in hospital practice ten times this dose could be used. Many more recent derivatives of chlorpromazine include "sparine" (promazine), phenelzine, "stemetil" (prochlorperazine), "stelazine" (trifluoperazine), and "melleril" (thioridazine). (2) Rauwolfia alkaloids—for example, "serpasil" (reserpine). On account of their hypotensive and depressive effects these substances were not suitable for general practice, but were used in the hospital treatment of schizophrenia. (3) Anti-hallucinatory drugs, especially "frenquel" (azacyclonol), and related substances. (4) Anti-anxiety drugs, such as "equanil" (meprobamate), "librium" (chlordiazepoxide), and "suavitil" (benactyzine). (5) Anti-depressants. Of these there were two main groups: (*a*) the amino-oxidase inhibitors: the original substance, "marsilid" (iproniazid), produced liver damage rather too often and too severely and had now been largely superseded by "niamid" (nialamide), "nardil" (phenelzine), or "marplan" (isocarboxazid); (*b*) "tofranil" (imipramine). This he found very useful, but it had many side-effects which had to be explained to both the patient and his general practitioner beforehand.

Dr. A. SPINKS (Macclesfield), as a pharmacologist and biochemist, agreed that the clinical classification given by Dr. Stafford-Clark correlated quite well with the biochemical structure and possible action of these substances. He explained that most derivatives of chlorpromazine had been developed in order to obtain drugs requiring a smaller dosage. Many of these substances were introduced after chance observations—for example, marsilid given in the treatment of pulmonary tuberculosis was shown to produce euphoria. Imipramine had been found to tranquillize animals. However, any explanations of action derived from animal experiments—for example, the way in which the amino-oxidase inhibitors interfered with serotonin—were plausible rather than reliable.

Use in General Practice

As a general practitioner, Dr. C. A. H. WATTS (Leicester) indicated that he found chlorpromazine particularly useful in elderly people who were becoming difficult and a little paranoid. He felt that schizophrenics should first be seen by a psychiatrist, and if the diagnosis was confirmed they should be admitted to a psychiatric hospital for high-dosage treatment, with the general practitioner later supervising maintenance. By contrast, the treatment of depressive illnesses should be first undertaken by the general practitioner. He used nardil for the first two weeks, and if this had no effect he instituted three to four weeks of tofranil. In the meantime, it was possible for the general practitioner to get to know his patient better, to make contact with his relatives, and to help the patient with his suicidal fears. Under this regime most depressive illnesses cleared up, he said, but if at the end of this period the depressive illness showed no sign of lifting, the patient should be referred to a psychiatrist, who would probably arrange for admission and/or electric convulsion treatment. He had found that 40% of patients responded to nardil, 50% responded to tofranil, and, in an earlier series, that 75% responded to E.C.T. Electric convulsion therapy

Panel Discussion on Tranquillizers. The panel from left to right, Dr. D. Stafford-Clark, Dr. A. Spinks, Dr. R. Hierons, and Dr. C. A. H. Watts.

therefore remained a more effective form of treatment than anti-depressant drugs, but its early use need not any longer be advocated, as so many patients responded to drug treatment.

The panel answered a considerable number of questions from the audience, and among the points which they were able to make were the following: Barbiturates were still useful in anxiety states, and some experienced general practitioners managed treatment with bromides without producing toxic confusional states. Tranquillizers had a different indication altogether, acting either by controlling delusional and hallucinatory experiences, aggression, or excitement, or by altering mood in depression. Some of these drugs produced jaundice and should never be used again once this had occurred, as fatal results might ensue. Parkinsonism produced by the drugs had always been found to be reversible. It was claimed that addiction was only very rarely produced but that habituation was often unavoidable in view of the long-standing types of illnesses that so often benefited by treatment with these substances. On the contrary it was important to dissuade patients from stopping medication as soon as schizophrenic or depressive symptoms, or anxiety, had been removed. In the case of depression, patients should be kept on a maintenance dose for two or three months and treatment reinstituted as soon as a recurrence threatened. Tranquillizing and anti-depressive drugs, which had also been found useful in the treatment of migraine, vomiting, and intractable pain, all tended to potentiate not only analgesics but also alcohol and barbiturates. Patients who were car drivers should be especially warned of this fact.

A view of the entrance to the Great Hall of the King's School.

PANEL ON MATERNAL MORTALITY

Under the chairmanship of Dr. ALAN BARKER (Whitstable) a panel discussion was held on the subject of "Maternal Mortality. Whose Responsibility?" Those on the panel were Dr. KATE HARROWER (general practitioner, Glasgow), Mr. T. L. T. LEWIS (obstetrician, London), and Dr. A. ELLIOTT (M.O.H., Maidstone).

The first question concerned the preventable causes of maternal mortality as mentioned in the Ministry of Health's *Confidential Enquiries into Maternal Mortality*. Mr. LEWIS pointed out that sepsis and haemorrhage were both largely preventable. With regard to haemorrhage he said that in order to prevent troubles there must be careful selection of vulnerable cases for hospital confinement; that a haemoglobin estimation should be done at an early stage of pregnancy—it was essential that all women with a low reading should be followed up energetically and effectively treated; that warning signs of a possible placenta praevia must be taken seriously; and that better facilities should be available for urgent blood transfusion at home as well as in hospital. Dr. HARROWER mentioned how difficult it was sometimes to persuade the vulnerable multigravida to go into hospital for delivery, and that often disaster occurred in these cases with no previous warning. A further difficulty in general practice was to decide when to send for the flying-squad or when to admit the patient who had suddenly collapsed. In the same context it was mentioned that it was not altogether fair to put all the blame on the doctor. In 24% of the deaths reviewed by the Committee the patient had not co-operated in regular antenatal attendance.

In reply to a question on the possible values of television and press propaganda for better antenatal care and co-operation, Dr. HARROWER was completely against this form of health education. Dr. ELLIOTT felt that there was already too much propaganda aimed at the mothers. Mr. LEWIS, on the other hand, thought that television was a good medium for public health education.

A questioner asked whether the Central Midwives' Board should insist that intramuscular ergometrine be given with the crowning of the head. All the panel thought it was quite wrong for anybody to insist on *any* therapeutic measure as a routine. Mr. LEWIS'S practice was not to use ergometrine routinely in normal cases but selectively when there was a previous history of post-partum haemorrhage, after forceps delivery, and after twins. All these cases should, in any case, be delivered in hospital. Discussing the use of oxytocic drugs, Mr. Lewis noted that in 33 deaths from ruptured uterus oxytocic drugs had been used in only three. He considered that while intravenous oxytocin was safe it should never be used intramuscularly. There was a very small place for injecting oxytocin (5–10 units) directly into the uterine muscle when all else failed with a post-partum haemorrhage. Mr. LEWIS and Dr. HARROWER both considered that there were more cases of retained placenta since the wide use of ergometrine than before, but at the same time there were fewer cases of post-partum haemorrhage, and the retained placenta could be removed with greater safety.

Discussing obstetric anaesthesia, Mr. LEWIS noted that maternal deaths from this cause were fortunately few and usually occurred from obstruction of the airway. All speakers agreed that domiciliary anaesthesia should always be given by a second doctor. In no circumstances should the same doctor attempt to supervise the anaesthetic as well as carry out a difficult delivery.

Flying-squads, in the opinion of the panel, should be the responsibilities of hospital boards, as they were now. They did not agree with a questioner that there was a need for a national flying-squad service. Each area had its own problems which had to be considered locally and individually. Mr. LEWIS said that hypofibrinogenaemia was a factor in haemorrhage in three possible situations: (1) in concealed accidental haemorrhage, where slow bleeding might go on continuously and dangerously; (2) where a dead foetus was retained: the patient should be admitted to hospital and careful control instituted with regular estimations of fibrinogen; and (3) with amniotic emboli: the patient suddenly collapsed with shock and post-partum haemorrhage. Treatment of hypofibrinogenaemia was by transfusion of fresh blood and intravenous injection of

2–10 g. of fibrinogen. Pulmonary emboli were the third most frequent cause of maternal mortality (14% of all deaths), but in the view of Mr. Lewis few of these could be prevented.

The final question referred to post-maturity. Dr. HARROWER doubted whether post-maturity really existed, and if it did the G.P. was in a quandary as to what to do and when to do it. Mr. LEWIS, on the other hand, believed that post-maturity was a factor in both maternal and foetal mortalities. His own policy was to recommend surgical induction in all primiparae over the age of 25 who were more than 42 weeks pregnant and where the foetal head was engaged.

CLINICOPATHOLOGICAL CONFERENCE

After tea, under the chairmanship of Dr. ALAN BARKER (Whitstable), a Clinicopathological Conference was held in the Great Hall at which Professor JOHN MCMICHAEL (London) was the guest speaker. The subject was a woman, aged 55 at death, a summary of whose case notes was previously circulated. Dr. G. B. FORBES (Canterbury) was the pathologist.

Professor MCMICHAEL went over the summary and evaluated the points which seemed to him salient and significant. He began by describing the case as a very difficult one, because signs and symptoms did not link up together. He noted that the patient had had winter bronchitis for many years, and that three years before her death she had developed multiple warts. These were treated by *x* rays, but at one of the sites, on one temple, a squamous-cell carcinoma developed which was excised without any recurrences appearing over the subsequent 2½ years. Eleven months before death the patient had developed another chest infection, and two months later she began to suffer from a series of widespread attacks of venous thrombophlebitis, as well as an episode of renal pain and tenderness. An intravenous pyelogram had shown no abnormality in the kidneys, but the *x*-ray films revealed areas of calcification in both thighs, which after exclusion of trichiniasis, scleroderma, and dermatomyositis were regarded as due to "idiopathic subcutaneous calcinosis of a metabolic type." Four months before death the patient became obviously ill with continuous swinging pyrexia, moderate anaemia with leucopenia, and a raised E.S.R. Numerous investigations were negative, but hilar shadows were seen on the chest *x*-rays. These became gradually more clearly defined and were attributed to enlarged lymph nodes. Marrow punctures, as well as examinations and cultures for tubercle bacilli, were negative. Three months before death the patient's spleen became significantly enlarged. She responded transiently to triamcinolone, one of the new steroids ("the modern aspirin" according to Professor McMichael), but soon the swinging temperature recurred, and the patient deteriorated and died.

In his final summing-up Professor McMichael proposed to accept the findings which relegated the calcinosis to the ranks of benign metabolic disorders, and he also accepted evidence supporting the assumption that the carcinoma had been excised and had not recurred. He thought, however, that the patient was definitely suffering from malignant disease, and that the enlarged and tender spleen placed the disorder in the class of the reticuloses. He demonstrated with the help of serial chest *x*-rays that there was not only enlargement of the hilar glands but also lymphatic obstruction, and this led him to diagnose the condition as a reticulosarcoma or a lymphatic sarcoma. The leucopenia would fit in with this, and recurrent thrombophlebitis was often due to malignant disease in middle-aged people. Raised alkaline phosphatase which was found towards the end of the illness might be due to involvement of the liver by the neoplastic process.

Members of the audience suggested various other possibilities, but none seemed equally acceptable, and no one anticipated the results of the post-mortem examination which were presented by Dr. G. B. FORBES. Up to the time of histological examination his findings appeared to support those of the clinicians. There was widespread enlargement of lymph nodes, which were white and necrotic, suggesting the diagnosis of reticulosarcoma. However, histological examination showed that the lymphatic tissue had been replaced by relatively acellular necrotic material in which Ziehl-Neelsen staining revealed myriads of tubercle bacilli. Similar foci were found in liver, spleen, and bone-marrow, and there were also widespread venous thrombi containing tubercle bacilli. In addition, there was an extensive bilateral suppurative pyelonephritis due to staphylococci, with staphylococcal micro-abscesses scattered through the myocardium. Death had therefore been due to tuberculous and staphylococcal septicaemia, and the case had been one of non-reactive tuberculosis, a condition not as yet easily recognized.

Dr. H. A TREBLE (Canterbury), under whose care the patient had been and who had thought on similar diagnostic lines as Professor McMichael, wondered if they had not been dealing with a case of reticulosis where secondary invasion with tubercle bacilli had occurred, because the patient's resistance had been lowered by steroid treatment. However, Professor MCMICHAEL felt that they could not very well take this way out, and said that he was returning to London a sadder but wiser man. No doubt most members of the audience felt the same.

PANEL ON ANAEMIA

Saturday, April 15

Under the chairmanship of Dr. I. B. MORRIS (Canterbury), a pathologist, a panel consisting of Dr. R. R. BOMFORD (London), general physician, Professor J. V. DACIE (London), haematologist, and Dr. ADRIAN M. SEMMENCE (Abingdon), general practitioner, dealt with questions on the "Investigation and Treatment of Anaemia in General Practice."

The panel all agreed that the adequate investigation of anaemias was now too complex for the G.P., and that what was really necessary for the G.P. was easy access to a laboratory where the investigations could be carried out for him. It was recommended that venous blood should be taken for tests and that it should be collected in clean, dry syringes (not necessarily boiled according to Dr. SEMMENCE, who sterilized them in strong cetrimide solution). Boiled syringes should be washed out in saline solution before use. The blood should be placed in a bottle with an anticoagulant such as the dipotassium salt of sequestrene or Wintrobe's oxalate mixture. At the same time as the blood was collected a smear should be made on a clean and dry slide (free of grease). The film should be spread by a smooth-edged spreader and fixed by drying in air. In an answer to a question on the reliability of the Tolqvist method, Professor DACIE reminded the audience that Tolqvist was a Swedish physician, and his method of comparing blood stains on blotting-paper with standards was very crude and only likely to be accurate to the nearest 20% figure. Neither he nor the other members of the panel could recommend it for general use, even as a screening test. In this discussion Dr. BOMFORD noted that, clinically, the physician could only get within 50% of accuracy by looking at the patient's mucous membranes and skin.

Anaemia in Pregnancy

Does "pregnancy anaemia" exist? This question was answered in the negative by Professor DACIE and Dr. BOMFORD, but Dr. SEMMENCE and the CHAIRMAN thought that it was a very important type of anaemia. Dr. SEMMENCE's routine treatment of combining folic acid with iron enabled him to get the expectant mother's haemoglobin up to 80% in all cases. He used folic acid from the 29th week of pregnancy. Discussion then centred on the use of folic acid. Professor DACIE felt that pregnant women were already over-bombarded with pills and he was not in favour of its routine use in pregnancy. Dr. BOMFORD was

apprehensive of its cost, but Dr. SEMMENCE pointed out that, given in the daily dosage of 20 mg. for 11 weeks (from the 29th week to term), the cost was only 10s.

Some disquiet was voiced in a question on the high proportion of positives in tests for occult blood in the faeces. Dr. BOMFORD tended to ignore the occasional "weak positive" and went all out to pick out the persistent "strong positives." Technically, Dr. SEMMENCE used a modification of the Gregersen method, and Dr. BOMFORD recommended confirmation by the older guaiac method. Turning to the question of how far the general practitioner should go in investigating his patients with anaemia, the views of Dr. SEMMENCE, the G.P., differed from those of Dr. BOMFORD and Professor DACIE, who work in hospitals. Dr. SEMMENCE was content to exclude serious bleeding by three negative occult-blood reports and then to await the response to adequate dosage with oral iron. The consultants looked on anaemia as a symptom and tried to investigate each case as fully as possible to discover the exact cause.

The use of "imferon" and "ferrivenin" in cases not responding to oral iron was questioned. In such refractive cases Dr. BOMFORD first tried to make certain that oral iron was in fact being taken by the patient (failure of the patient to take the iron tablets was the most usual reason for failure of an iron-deficiency anaemia to respond). In those cases where oral iron had been taken without response he used imferon or ferrivenin. He preferred the latter, because imferon tended to be painful, to cause staining of the skin, and there was some risk of carcinogenesis. Although colour indices had been important in the past, the panel did not think that they were of any value now in the diagnosis of anaemias. In defining the type of an anaemia the results of many investigations had to be taken together. The CHAIRMAN considered that the red-cell count was open to many errors, and, while Professor DACIE agreed, he did think it was of real value in polycythaemia. New electronic methods of blood-cell counting were costly, but saved a great deal of time.

Use and Abuse of Vitamin B_{12}

Certain practical procedures were raised by a question on whether vitamin B_{12} was ever justified in an incompletely diagnosed case of anaemia. Dr. BOMFORD thought that only very exceptionally should vitamin B_{12} be used without an accurate diagnosis first being made. He would do so in an elderly patient with severe anaemia who refused to be investigated. The other members of the panel agreed. The CHAIRMAN pointed out that an injection of vitamin B_{12} would completely alter the peripheral blood picture within four hours and make diagnosis extremely difficult. A member of the audience pointed out that vitamin B_{12} was a constituent of a "tonic" on sale to the public, and raised the question whether this substance should be a scheduled preparation. As a cause of psychiatric symptoms the panel considered that megaloblastic anaemias occupied a very small place, but that where there was any clinical suspicion of anaemia a blood count and smear were urgently indicated. Although there was evidence that oral preparations of vitamin B_{12} were effective in maintaining patients with pernicious anaemia, the panel did not recommend this as reliable. The indications for the use of thyroid, ascorbic acid, hydrochloric acid, and other vitamins were only in specific disorders. Thus thyroid preparations were effective only in hypothyroid states and vitamins only in disorders where the deficiency was proved. Hydrochloric acid had no beneficial effects and the haphazard use of vitamins was useless, although Dr. SEMMENCE said that, in his opinion, vitamin deficiencies were frequent in old women.

In treating iron-deficiency anaemias, Dr. Semmence first used ferrous sulphate, and if there were any side-effects he then changed to ferrous gluconate or ferrous fumarate. In answer to a question regretting that haematologists were monopolizing the management of anaemias, the panel felt that this state of affairs had to be accepted, as the subject had advanced so rapidly.

TAPE-RECORDINGS IN GENERAL PRACTICE

The use of audio-visual aids in the difficult task of keeping busy general practitioners up to date with modern methods and concepts in medicine was demonstrated by Drs. JOHN and VALERIE GRAVES (Writtle) at a general session on Saturday morning. They had made tape-recordings of talks by specialists in various fields of medicine, which they circulated to small groups of general practitioners who met to hear them and discuss the clinical problems presented. Extracts from such tape-recordings were played through at the session, and the speakers demonstrated the value of projecting colour transparencies to augment the sound record. Since the start of this venture, which was associated with the College of General Practitioners, with 27 volunteers in 1957, the number of regular listeners who now get recordings sent to them every two months had increased to 300. Last year 680 recordings from the library were sent out to small groups, and it was estimated that over 1,000 practitioners heard these talks. There were many overseas listeners in countries as far afield as Jamaica, Queensland, and Israel. It was possible to have a recorded discussion, as was demonstrated at the session. A speaker introduced a subject and comments were made by doctors in their own homes, who then forwarded the tape to interested colleagues. Dr. John Graves also demonstrated the use of a portable tape-recorder and camera in general practice by showing transparencies of his own cases and by playing recordings of various clinical sounds such as cardiac murmurs and the typical paroxysmal cough of whooping-cough. This session was very well received by an appreciative audience.

TELEVISION, FILMS, AND EXHIBITIONS

There were two sessions of colour television, arranged in conjunction with Smith Kline and French, relaying clinical demonstrations and surgical operations from the Kent and Canterbury Hospital to the Great Hall of King's School. On Friday morning the programme included the operation of patellectomy in a patient with early osteoarthritis of the knee-joint. The surgeon, Mr. F. G. ST. CLAIR STRANGE (Canterbury), and his anaesthetist, Dr. N. P. READ (Canterbury), gave a commentary on the operation; comments and questions were discussed by a panel under the chairmanship of Dr. A. D. O'CONNOR (Canterbury) consisting of Mr. P. R. WRIGHT (Broadstairs) and Mr. E. BARBER, the remedial gymnast to the Kent and Canterbury Hospital. The technical side of the operation was well demonstrated, and a patient who had previously undergone a similar procedure was shown to have full movement of the knee-joint following physiotherapy. Dr. H. A. TREBLE (Canterbury) demonstrated dermatological cases of general medical interest. He showed two patients with generalized scleroderma and a case of xanthomatosis. These cases were discussed by Dr. D. E. SHARVILL (Hythe) and Dr. J. A. GLOVER (Folkestone), under the chairmanship of Dr. A. D. O'CONNOR. A retropubic prostatectomy was performed by Mr. EDGAR FRESHMAN (Canterbury), and on the panel discussing the operative procedure were Mr. B. G. A. LILWALL (Broadstairs) and Dr. C. R. KIRKPATRICK (Broadstairs). Dr. J. R. FORSAITH (Canterbury), the anaesthetist at the operation, commented on the use of hypotensive anaesthesia during prostatectomy as being a safe and expedient procedure. During the programme questions from the hall were relayed by the moderator, Mr. T. A. CLARKE (Canterbury), and answered by the operators and members of the panel.

In the second session, on Saturday morning, the operation of myomectomy was demonstrated by Mr. J. WARD (Canterbury), before he went on to perform a hysterectomy because of the patient's excessive menorrhagia. The anaesthetist, Dr. R. H. BLAZEBY (Ramsgate), gave details of the anaesthetic, and the chairman of the panel, Mr. LILWALL, introduced Miss JEAN R. C. BURTON-BROWN (Canterbury) and Mr. M. PETER DURHAM (Folkestone), who discussed the

problems related to myomata and the indications for myomectomy. Paediatric patients of clinical interest were demonstrated by Dr. T. S. RODGERS (Canterbury) and discussed by the panel consisting of Dr. R. HIERONS (Canterbury) and Dr. K. E. SPITTLEHOUSE (Ramsgate) under the chairmanship of Mr. LILWALL. The cases demonstrated were a patient with hypoglobinaemia, and three children with muscular weakness due to different causes. The surgical operation of vagotomy and gastro-enterostomy was performed by Mr. R. L. CANNEY (Canterbury), who demonstrated the value of the electrical stimulation of the oesophagus and the recording of the motility of the stomach after vagotomy as a check on the completeness of the vagal section. Dr. N. P. READ, who gave the anaesthetic, demonstrated the apparatus. Mr. M. R. WILLIAMS (Canterbury) and Mr. D. V. EVANS (Folkestone), who formed the panel under the chairmanship of Mr. LILWALL, discussed the merits and contraindications for the operation of vagotomy and gastro-enterostomy as opposed to partial gastrectomy. During the session of the proceedings Mr. CLARKE again acted as moderator in the Great Hall.

Medical Films

The medical films, of which there were two showings at the Meeting, were introduced by Dr. R. PROSPER LISTON, the chairman of the B.M.A. Film Committee. He said that the B.M.A. had selected complete programmes of films for the use of local Branches, and that these could be borrowed on application. Five films were shown, of which the first four were available from the library. These are listed below with the names of the medical and production authorities in parentheses after the title. All the films were in colour and all but the last had sound commentary.

(1) "Upper Lobectomy with Sleeve Resection of the Main Bronchus" (Sir Clement Price Thomas; Royal Society of Medicine). The difficult technique of this lobectomy was well described and the photography was excellent. (2) "Aneurysm of the Abdominal Aorta" (Dr. K. D. Keele; Wellcome Foundation, Ltd.). This film gave an excellent account of the cause, presentation, and natural history of this condition. The commentary and diagrams were excellent. (3) "Claremont" (Bristol Public Health Department; Bristol Amateur Cine Society). This film won a B.M.A. film competition against 70 entries. It dealt with the treatment of children affected by cerebral palsy. Both photography and commentary were good. (4) "Current Ophthalmic Surgical Technique" (Mr. P. D. Trevor-Roper and Dr. Peter Hansell; Department of Photography and Illustration, Westminster Medical School). The treatment of cataract, glaucoma, and retinal detachment was dealt with briefly. The photography was outstanding. (5) "Early Rehabilitation of Fractures of Femoral Shaft" (Mr. F. G. St. Clair Strange). This film was in colour but was silent. It demonstrated the wide range of movements that a patient in a Thomas splint could practise with safety. These included standing and sitting out of bed, swimming, and climbing to the top of the cross-bars.

Exhibitions

During the meeting the British Red Cross Society mounted a useful exhibition of domestic aids for the disabled at the Red Cross Hall. In the King's School there were three exhibits to supplement the programme: Dr. L. A. Gibbons's (Reigate) ingenious animated displays of the circulatory system (including a display of foetal cardiac abnormalities), an exhibit by the Medical Groups of the Royal Photographic Society and the Institute of British Photographers on the applications of photography to general practice, and an exhibit on tape recordings in general practice by Drs. John and Valerie Graves (Writtle).

CLINICAL DEMONSTRATIONS

On Saturday afternoon clinical demonstrations were held at the Kent and Canterbury Hospital and at St. Augustine's (Psychiatric) Hospital, Chartham.

Kent and Canterbury Hospital

The Kent and Canterbury Hospital is a pleasant hospital, especially on a sunny April afternoon, modern (1937), and well appointed. Mr. F. G. ST. CLAIR STRANGE's master-plan divided the available space on the ground floor into four main geographical areas, or circuits, each distinguished by a separate colour, with which corresponded the colour of the cards brought by the patients who were summoned for demonstration. In each circuit three sessions of three-quarters of an hour took place, with different consultants demonstrating a different set of patients at each session; the remaining quarter of each hour was used for the change-over of patients and for rest, cups of tea, and a smoke for the doctors. The case-summaries were successfully stylized and were presented uniformly typed on the inside of a quarto folder with reduced negative prints of relevant *x*-rays arranged opposite them. The smooth execution of this plan concealed a vast amount of detailed preparation and depended to a great extent on highly efficient staffing by a corps of sisters and nurses, with the ancillary staff of the hospital giving their services as ushers and stewards and the domestic staff looking after everybody's comfort; the co-operation of the ambulance services—on a Saturday afternoon—was exemplary.

The clinical material mostly followed orthodox lines and was of good quality. Case demonstrations and short ward rounds were interspersed with static or inanimate displays, for instance, of calculous disease by the pathologist, of bone-tumours and the radiology of the oesophagus, of models displaying causes of pain in the temporo-mandibular joint. The new cobalt unit aroused a good deal of interest (the cobalt arrived just in time), group-therapy for Parkinsonism was impressive, and Dr. AUDREY CAREY's locally produced film on "Rehabilitation for Day-to-Day Activity in the Home" deserves special mention. A total of 43 demonstrations were spread over the three sessions, and it is impossible to describe them in detail. One visitor was heard to remark that he could happily have spent a whole day instead of an afternoon on the clinical material provided.

St. Augustine's (Psychiatric) Hospital

In the Cathedral a stained-glass window shows a madman being brought to heel by corporal punishment—at least so the superscription *Amens Accedit* assures us. At St. Augustine's Hospital, Dr. J. A. AINSLIE and Dr. G. P. HARTIGAN welcomed their visitors to a demonstration of modern treatments in psychiatry. Members of the medical staff had set out exhibits to illustrate various aspects of depressive illness, and were present to explain and discuss them with their visiting colleagues. Patients were there too, and they seemed to be equally willing to describe their therapeutic experiences.

Dr. K. J. TILLING and Dr. P. H. MITCHELL demonstrated the symptomatology of depression, and especially the problem of suicide, in a striking fashion, and Dr. P. J. F. AARONRICKS and Mr. JOHN LINDSAY presented ways in which dementia and depression can be differentiated from one another in elderly people. Depressive illness affects different people in a variety of ways, and therefore widely differing methods of treatment may be applicable. Recurrent affective illnesses in the setting of neurotic personality difficulties often respond best and more lastingly to psychotherapy. This point was made by Dr. H. JOHN HAMBLING in a demonstration of the psychopathological content and of progress during analytical treatment facilitated by lysergic-acid abreactions. Dr. R. H. V. OLLENDORFF presented a historic survey of the drug treatment of depression, and showed patients exhibiting a number of undesirable side-effects. Any family doctor who still felt that electric convulsion therapy was a frightening or barbarous procedure should have had these ideas dispelled by the smooth, reassuring, and gentle way in which electroplexy modified by suxamethonium and given under thiopentone anaesthesia was administered by Dr. T. A. R. CALLENDER and members of the hospital staff. Finally, Mr. GEOFFREY C. KNIGHT

showed that in the last resort, if all the preceding methods of treatment have failed, leucotomy holds out a fair chance of success. He had been especially concerned to avoid unpleasant personality changes by placing small cuts at open operations, and he now favours a restricted orbital undercutting procedure, ultimately to be carried out stereotaxically.

The topical subject of community care was illustrated in a series of exhibits by Dr. E. A. RITCHIE. Of special interest were a number of patients doing several unskilled and semi-skilled assembly and dismantling jobs. They were representative of some 150 patients attending workshops in the hospital and doing paid work provided by five industrial firms and two Government departments. It was suggested that, beyond the benefit of regular occupation, this demonstration to the patient of his earning power was of therapeutic import not only in long-stay but also in recent cases.

Another new development at St. Augustine's Hospital is an adolescent unit for 16 boys between 12 and 16 years of age. The problems they presented, and the ways in which they were treated, were put over very clearly by Dr. G. C. TURLE and Mr. C. WOOLLEN, the child psychotherapist. While encouraging self-expression, strikingly demonstrated in the use made of a "smear room," they believe that discipline is necessary too. All the members of the staff are used to get these young patients to respond positively to adults, and in this way are helped with their own disturbed attempts to become adults.

CATHEDRAL ARCHIVES

Three medical items were among the ancient documents shown in the Cathedral Library by the archivist, Dr. WILLIAM URRY, on Friday and Saturday morning. One was a recently found contemporary copy of the Folkestone Parish Register for 1578 containing the entry of William Harvey's baptism on April 6. The other two documents related to early G.P.s of Canterbury: one, the oldest-surviving local borough survey (*c.* 1166), noted that "Petrus Medicus" had paid his mid-Lent rent of 12d. and a 3½d. labour-service charge to the Cathedral monks. He and his son John, also a doctor, must have been done out of a considerable amount of business by Becket's shrine, said Dr. Urry. Godefrid the baker, whose name appeared frequently in records of this time, had three sons, all of whom were cured by the touch of a rag dipped in Becket's blood. The shrine accounted for large numbers of cures, and the annual list of takings (from pilgrims) kept by the monks showed £94 for the shrine alone in 1261–2. Another medical man was Magister Feraminus, M.O.H. to the monks, whose name appeared in a monastic register for 1189. He was prone to visions and through his political activities fell foul of Henry II.

Other documents included a parchment bearing the marks of William the Conqueror and Queen Matilda and dated Easter, 1072, in which Lanfranc, Archbishop of Canterbury, persuaded several bishops to agree to his superiority over York; Thomas of York himself added a reluctant "*concedo*" to his signature. A small piece of parchment with a large seal was the penance of Sir William De Tracy, one of the four murderers of Thomas Becket, granting the manor of Daccombe in Devon to Canterbury, and sustaining a monk perpetually praying in the Cathedral for the De Tracy family. A romantic connexion with Tudor times was a rosebud found in the City Plea Roll at the page containing the last of many entries relating to the family of Christopher Marlowe, shortly before his murder in 1593.

SOCIAL OCCASIONS

The Civic Reception given by the MAYOR OF CANTERBURY on the first evening of the Meeting was noted in the first part of our report. On Friday evening the East Kent Division gave a most successful Wine and Cheese Party at the impressive new Frank Hooker School. The guests were received by Dr. I. H. K. STEVENS, chairman of the Division, and Mrs. STEVENS. On Saturday evening Messrs. Pfizer Ltd. sponsored a concert by the Boyd Neel Orchestra, conducted by Mr. RAYMOND LEPPARD, in the Great Hall of King's School. Works by Handel, Mozart, Warlock, Wirén, and Britten were played to a large and enthusiastic audience. Earlier in the evening the Christian Medical Fellowship held a Buffet Supper at "The Pilgrims," under the chairmanship of Mr. D. F. ELLISON NASH, at which Mr. S. FARRANT RUSSELL spoke.

On Sunday there were Matins in the Cathedral, where Canon A. O. STANDEN was the preacher, and Principal Mass at St. Thomas's Roman Catholic Church. Golfers were catered for at Prince's Golf Club, Sandwich, Canterbury Golf Club, and the Royal Cinque Ports Golf Club, Deal. The Whitstable Yacht Club offered hospitality, and at least one medical visitor had a most enjoyable sail in a Flying Dutchman. In the afternoon there was a small ceremony in Folkestone, where wreaths were laid at the foot of William Harvey's statue by Dr. A. TALBOT ROGERS, Chairman of the Representative Body, Dr. E. R. CULLINAN, representing the Harveian Society of London, and the MAYOR OF FOLKESTONE.

Ladies' Programme

An excellent social programme for the ladies was arranged by Mrs. I. H. K. STEVENS. On Friday a large party was entertained to lunch by Messrs. Pfizer Ltd., and then taken over Dover Castle and the Pfizer works at Richborough. Dr. BERTHA BRIANT led a tour on Thomas à Becket, and there was a visit to a notable private art collection. These tours were followed by a tea party attended by 71 ladies. On Saturday there were interesting tours of the Cathedral and the city, and Dr. WILLIAM URRY, the archivist, lectured in the Cathedral library. Local hostesses entertained 30 ladies to lunch, and in the afternoon there was a demonstration on the art of make-up by Messrs. Lancôme from London. This was followed by tea which, as on Friday, was kindly provided by the local Division of the British Medical Association.

THE AFTERCARE OF THE HOSPITAL PATIENT*

BY

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The subsequent experience of patients treated in some Scottish hospitals is the subject of this report. In the west, our original work was based primarily on 705 men treated in the general medical wards of four hospitals for acute cases; they were seen in hospital and visited in their own homes over a period of two years after discharge. The mean age of the patients was 49 years; 18% were over 64.

The wards involved treat many very seriously ill people, as may be judged from the fact that the immediate ward mortality is about 15%. Within the five years preceding the admissions with which we were concerned, 22% of the patients studied had already had in-patient treatment for the same or a related condition, while, in addition, 12% had had out-patient hospital care. The readmission rate was especially high among those suffering from diseases of the blood, digestive system, and circulation.

The clinician in charge classified just over 9% of those patients on discharge from hospital as "cured" and

*Paper read to the Section of Preventive and Social Medicine at the Joint Annual Meeting of the British Medical Association and the Canadian Medical Association, Edinburgh, 1959.

73% as "improved"; he estimated that 40% were likely to be fit to return to their own job within three weeks of leaving hospital and a further 3 to 4% fit for alternative employment.

Employment After Discharge

Within three months of leaving hospital, 9% of the patients had died and 5% were readmitted; 64% continued to improve, 24% remained very much as on discharge, still far from well, and 11% had clearly deteriorated; so that roughly one in four had gone downhill. At the end of three months 61% of the survivors between the ages of 15 and 64 were back at work, but fully one-fifth of them were in jobs that could only be regarded as unsuitable. The proportion in unsuitable work was high among lads between the ages of 15 and 19 (often suffering from heart disease) and at ages over 50, many of the latter also being cardiac cases. Of men registered as handicapped under the Disabled Persons (Employment) Act, only 32% were in employment three months after leaving hospital. The proportion of men back at work after three months did not correspond closely with the clinician's estimate of fitness for early return; it was much more closely related to home conditions and nature of employment.

Nor was the picture any brighter two years after the patients left hospital. By that time 26% had died; 47% had maintained the improvement initiated in hospital; 16% were classified as "condition unchanged," still far from established good health; and 10% had deteriorated. Rather less than two-thirds of those still alive had derived substantial and lasting benefit from hospital care. In the course of these two years 27% of the survivors had been readmitted to hospital on at least one occasion. Over a period of seven years—the five preceding the admission on which the study was based and the two following it—48% of the survivors had at least one other spell of hospital treatment and fully half of these had two or more additional spells.

Two years after leaving hospital 27% of the survivors were not in employment; the proportion not at work was nearly twice as high among the men who had been unskilled labourers as among those who had been in non-manual jobs. Just under 20% of those who were working were in jobs regarded as unsuitable; the proportion in unsuitable work was highest between the ages of 45 and 64, and rather higher among men who had taken up new work after their illness than among those who had returned to their old job. Of those who were alive two years after leaving hospital, 22% had done no work during that period and a further 10% had worked for less than one of the two years.

Causes of Breakdown

So much for the bare facts, which can only be regarded as disappointing. For most patients hospital care is but an episode in a very much longer tale of medical supervision. Transition from the sheltered atmosphere of the modern hospital ward to the icy chill of the workaday world is a testing time, and it is not surprising that many soon break down; in our series relapse often came from bad social and environmental conditions rather than from any inevitability on medical grounds.

Sometimes the work itself was grossly unsuitable, either from its nature or from the circumstances in which it was done, having regard to the man's condition; sometimes the trouble arose from unhappy relations with foreman or workmates. On leaving hospital, far too many men returned to jobs which could scarcely fail to precipitate another breakdown in the not-far-distant future. The non-manual worker is fortunate in that he can usually go back to his own job. The skilled worker unable to continue at his trade has a good chance of finding non-manual work; but for the unskilled labourer the choice is often between a pick and a shovel, and, not surprisingly, the proportion unemployed two years after leaving hospital was about twice as high among the unskilled as among the others.

The hospital physician estimated that the breakdown in health that had led to admission was preventable in 10% of cases—mostly cases in which the patient suffered from some acute intoxication or in which he had been grossly remiss in his observance of the way of life demanded by the medical condition from which he was known to suffer. Instances of this are the case of the patient with peptic ulcer who committed some major indiscretion of diet; that of the diabetic who did not continue with the balanced insulin treatment which had been mapped out for him; and, less often, that of the patient suffering from pernicious anaemia who failed to continue his prescribed therapy. These patients were not drawn from any particular age-group, but included a relatively high proportion of unskilled manual workers.

When the men were seen in their own homes, it soon emerged that the breakdown that had taken them to hospital was in some cases the direct outcome of bad social, economic, or environmental circumstances—such as grossly defective housing, lack of adequate home care, or patently unsuitable work; 15% of the cases studied could be classified as falling into this group, so that in about 25% of cases a major preventable factor of one kind or another could be regarded as being present. Nor does this figure of 25% exhaust the tale of cases in which social or environmental factors contributed to breakdown or interfered with recovery; these contributory social factors were mainly associated with employment, and assumed greatest importance between the ages of 45 and 64.

It was estimated that only about one-third of the patients given advice calculated to prevent relapse could be counted upon with reasonable certainty to accept the advice given to them. Some of this unwillingness to accept advice could be traced to reluctance to give up a job or a way of life to which the patient had become accustomed or which he liked, but many who knew that their job was beyond their strength were unable to find one more suitable.

Bridging the Gap

In the nature of things, much devoted and highly skilled hospital treatment can have little prospect of restoring effective working capacity, for many patients on admission are already gravely, even hopelessly, ill; but our experience leads us to ask what can be done to obtain a greater measure of permanent benefit from hospital care. Much depends on the part which we wish hospitals to play in the Health Service. Some could, with profit, undertake a greater measure of constructive work than at present; there is much scope for the hospital as a diagnostic centre in the early, more promising stages of disease, and the best hospitals might well take a larger place in helping to shape the careers

of young disabled persons. Under present conditions, with so many with established illness clamouring for admission, this may sound Utopian. It is certain that, assuming continuance of the present pattern of hospital admission, we are lamentably short of convalescent accommodation—especially the kind of graded convalescence which has the express object of restoring capacity for work and bridging the wide gap between hospital ward and everyday life.

Until we provide conditions which give a man a reasonable chance of maintaining the improvement which hospital care has initiated, a large fraction of costly in-patient treatment can only be the merest palliative patchwork. Much of our housing is still grossly unsatisfactory, though it is being improved; many invalids lack the kind of benevolent home background that so often makes all the difference between progress and relapse. The State has set up machinery to help the handicapped to find suitable jobs, but many disabled men, especially unskilled labourers, cannot get suitable work even in time of relatively full employment.

The simple fact is that, in Scotland at all events, effective aftercare is yet only in its infancy, so far as the common major illnesses of the people are concerned; and it very badly needs development if the work of the hospitals is not to continue to be speedily undone. Integration is an overworked word, but it is not too much to say that lack of effective integration of health and social services can be disastrous for the welfare of the patient. We must do more to help the family doctor in his struggle to keep the patient on his feet, and more to encourage the patient to try to follow a way of life that will be satisfying to him and within his compass. It is important to preserve all that is best in our hospital tradition, but equally it is important to try to view hospital care in true perspective.

During the past few years we have been working with another similar group of patients discharged from acute medical wards in Glasgow to find out whether, by the energetic use of all the statutory and voluntary agencies available in the city, we can help to obtain better results than those described earlier in this paper. We have certainly been able to help some patients, but what proportion is not yet clear. Before long we should be able to assess the results objectively—to judge not merely the measure of our success but the reasons for our failures; and the results may help to lend promising direction to aftercare.

OPHTHALMOLOGICAL SOCIETY OF U.K.

DR. IDA MANN'S BOWMAN LECTURE

[FROM A SPECIAL CORRESPONDENT]

The Ophthalmological Society of the United Kingdom held its 81st Annual Congress at the Royal Society of Medicine from April 13 to 15. The meeting included a symposium on "The Late Complications of Aphakia," a discussion on "Neovascularization in Ocular Disease," the Bowman Lecture, and various papers.

Anthropology and Pathology

This year's Bowman Lecture was delivered by Dr. IDA MANN, who left her chair in ophthalmology at Oxford 12 years ago to practise in Western Australia; and the subject of her talk, "Climates, Cultures, and Eye Disease," derived from her interest during these last 12 years in the country and people of her adoption. Her thesis, which, as she said, could as well have been titled "Anthropology and Pathology," underlined the relationship of disease to the varying habits and climates of peoples who were separated by the accidents of geography—a study that had been too long neglected, and which yearly became more difficult as geographical barriers receded and man's energies were directed more to cope with his cultural than his physical environment.

The naked influence of climate in determining the nature of the food supply (proportion of animal to vegetable matter) and parasites (incidence of insect vectors) was in fact generally overridden by that of culture (the habits of the previous tribes that immigrated into any particular region)—whether the race was settled or nomadic, rice- or cereal-eating, wearing wool or leather, etc. Thus, the incidence of infectious diseases like trachoma was greater in Muslim communities, where it was furthered by the use of cosmetics and by the seasonal pilgrimages to Mecca through the most highly infected countries in the world. Religion likewise might promote genetic diseases by placing limitations on the persons with whom marriage was permitted; it might encourage eccentric habits resulting in anaemia like the ritual blood-letting in the Wongada tribe no less than the refusal to accept transfusion by Jehovah's Witnesses; or there might be taboos on rational treatment such as were found alike in primitive tribes and among sophisticated Christian scientists.

Application to Eye Disease

In applying her thesis to eye diseases, Dr. Mann first considered the incidence of convergent squint. Among full-blooded Australians, who were practically all hypermetropic, and most of whom were intermingled with the European stock, sharing their education and diet, convergent squint was apparently unknown, while about 2% of the white population was so affected, half of these having a hereditary basis. This would suggest an underlying anatomical causation—in contrast to divergent squint, which was much more regularly distributed among different racial groups. Similarly, myopia was virtually confined to the white population (4.8% of causes of blindness), while its frequency was double this figure in England, and greatest of all in Malta. Glaucoma, too, was almost absent from the aboriginals of Australia and New Guinea (1% of blindness in contrast to 13.6% in England). Iceland had the highest incidence of hereditary glaucoma, 47% of their cases of glaucoma having a genetic basis.

The incidence of cataract was often thought to be greater in the tropics, although there was little statistical support for this, and endocrine or nutritional factors might well determine its frequency in different countries. The varying incidence of uveitis, too, reflected many factors that were difficult to assess, the incidence of onchocerciasis being affected by clothing habits, and of toxoplasmosis by the domestic animals employed; however, the Australian aboriginals had a surprising freedom from sympathetic ophthalmitis, in spite of an ample supply of untreated perforating wounds. The distribution of trachoma had excited much interest in the past, and its spread by man's migrations reflected again and again the wars and religious fervour of past centuries, just as its incidence in the wake of these human tides reflected the habits of the tribes it infected.

Many other eye diseases also lent themselves to a rewarding geographical analysis, such as the various nutritional diseases that so directly depended on the natural foods in a district, the high incidence of pterygium and pingueculum on the bright sandy coastline of Western Australia (but equally in the dark jungles of Brazil), and the spread of varying patterns of virus conjunctivitis. For the study of geographic pathology was as wide as the whole world, and as limitless as time.

London County Council now authorizes 687 chiropody sessions a week as against 587 sessions a week in January, 1960, and 487 sessions a week in January, 1959. (L.C.C. Council Meeting, February 14.)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

NON-VIRILIZING ANDROGENS

Stanolone
"Anabolex" (Lloyd-Hamol) = 17β-hydroxyandrostan-3-one.

Oxymetholone
"Anapolon" (I.C.I. = 17β-hydroxy-2-hydroxymethylene-17α-methylandrostan-3-one.

Mestanolone
"Androstalone" (Roussel) = 17β-hydroxy-17α-methylandrostan-3-one.

Methandienone
"Dianabol" (Ciba) = 17β-hydroxy-17α-methyl-$\Delta^{1,4}$-androstadien-3-one.

Nandrolone
"Durabolin" (Organon) = 17-hydroxy-Δ^4-19-norandrosten-3-one β-phenylpropionate.

Norethandrolone
"Nilevar" (Searle) = 17β-hydroxy-17α-ethyl-Δ^4-19-norandrosten-3-one.

Methylandrostenediol (chemical name)
"Protandren" (Ciba) = 17β-methyl-Δ^5-androsten-3β, 17α-diol.

"Stenediol" (Organon) = same as above.

Chemistry.—These compounds may be regarded as derivatives of testosterone. The Table below shows that all are chemically closely related.

Pharmacology.—Non-virilizing androgens is not the happiest name for this group of substances: if given in big enough doses and for a sufficient time all of them will produce some virilization. It can, however, be shown that the ratio of their anabolic to androgenic potency is significantly higher than that of testosterone. The ratio varies considerably but may be very high—for example, compared with testosterone phenylpropionate that for nandrolone is 8:1, and that of norethandrolone related to testosterone propionate is 15:1. The anabolic effect of these steroids has been measured by the increase in the body-weight of male and female rats, in which they can also be shown to antagonize the katabolic action of cortisol or cortisone. Some of the anabolic steroids have a hysterotrophic action; it seems to be a direct effect on the uterus, since it occurs in spayed animals. Moreover, as estimated by the Clauberg test (development of the uterine mucosa in oestrogen-primed immature rabbits), some of these compounds have progestational activity which may be stronger than that of progesterone itself. Norethandrolone, for instance, is about 10 times as active as progesterone and has been shown to be an effective antifertility agent in female rats. Its use in women is contraindicated during the first trimester of pregnancy. A progestational effect of nandrolone has been shown in rabbits, while methandienone seems to have virtually none.

Therapy.—These steroids have been given for many conditions in which protein-anabolic or anti-katabolic effects seem desirable. More specifically, the following indications have been suggested: (1) Treatment of emaciated or asthenic patients—for example, children with tropical asthenia, chronic alcoholics, and women with hyperemesis gravidarum. (2) Stimulation of growth in children and premature infants. The anabolic steroids have been used in such cases when growth hormone was not available. (3) In muscle-wasting diseases (poliomyelitis, quadriplegia, or bed-ridden patients with decubitus ulcers). (4) After surgical intervention or during recovery from severe burns to prevent prolonged negative nitrogen balances. (5) Prevention or treatment of the katabolic effects of intensive therapy with glucocorticoids (in Addison's disease, panhypopituitarism, and, in selected patients, after adrenalectomy or hypophysectomy). (6) In acute or chronic renal failure to reduce the concentration of blood urea despite an increase in the amount of dietary protein.

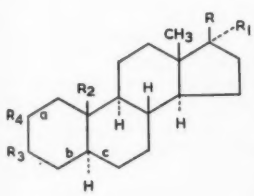
Since the protein-anabolic action of these steroids is linked with calcium retention, they have also been prescribed for the prevention or treatment of osteoporosis in patients treated with corticosteroids or their synthetic substitutes and in post-menopausal or senile women.

Some of these indications—while perhaps theoretically justifiable—have clinically not been sufficiently explored. The high cost of treatment with the non-virilizing androgens should be borne in mind, particularly when the indications for their use are not strictly specific.

Dosage will partly depend on the results of nitrogen-balance estimations and on plasma-calcium levels. The doses recommended by the makers are: *Anabolex*, 50–75 mg. daily (adults), sublabially or sublingually. Courses of 15–20 days per month are given. *Anapolon*, 5–15 mg. by mouth daily (adults) for 30–45 days with breaks of 10–15 days between courses. *Androstalone*, 25–50 mg. daily, sublabially or sublingually, for 12–18 days with intervals of two weeks between courses. *Dianabol*, 15–20 mg. by mouth daily (adults); maintenance dose, 5–10 mg. daily. *Durabolin*, 25 mg. by intramuscular injection once weekly. *Nilevar*, orally: 20–30 mg. daily (adults); intramuscularly: 25 mg. daily; interval of one month after three months' treatment. *Protandren*, 25–50 mg. per day sublingually (adults). *Stenediol*, 10 mg. by mouth three times a day after meals (adults).

Side-effects.—Slight virilizing effects—for example, deepening of voice—may occur but are rare with the doses recommended. (The virilizing activity of methylandrostenediol seems to be more prominent than that of the more recently introduced anabolic steroids.) Treatment with any of these compounds is contraindicated in patients with prostatic carcinoma. Fluid retention has been observed, particularly in patients with circulatory or renal diseases. The progesterone-like activity of some of the compounds has already been mentioned. Withdrawal bleeding may follow a course of norethandrolone in post-menopausal women, and menorrhagia, irregular menses, or amenorrhoea has been reported in young women. Hypercalcaemia may occur occasionally. The incidence of jaundice, which—though rarely—may occur after treatment with methyltestosterone, will have to be watched. If it occurs, immediate withdrawal of the steroid is indicated.

N.H.S. Basic Price.—Anabolex, 100×25 mg. tabs., 64s. Anapolon, 100×5 mg. tabs., 68s. Androstalone, 100×25 mg. tabs., 82s. Dianabol, 100×5 mg. tabs., 43s. 7d. Durabolin, 25 ampoules (25 mg./ml.), 167s. 4d. Nilevar, 100×10 mg. tabs., 129s. 4d. Protandren, 100×25 mg. linguets, 58s. 2d. Stenediol, 100×10 mg. tabs., 23s. 10d.



	Groups					Bonds S=single. D=double		
	R	R_1	R_2	R_3	R_4	a	b	c
Stanolone	OH	H	CH_3	O=	H_2	S	S	S
Oxymetholone ..	OH	CH_3	CH_3	O=	HOCH=	S	S	S
Mestanolone ..	OH	CH_3	CH_3	O=	H_2	S	S	S
Methandienone ..	OH	CH_3	CH_3	O=	H	D	D*	S
Nandrolone	$OCO.CH_2.CH_2.C_6H_5$	H	H	O=	H_2	S	D*	S
Norethandrolone ..	OH	$CH_2.CH_3$	H	O=	H_2	S	D*	S
Methylandrostenediol	CH_3	OH	CH_3	HO(α)	H_2	S	S	D*

* No H at C_5

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Acute Diabetic Abdomen

SIR,—I am glad to see that Dr. P. Edward Dipple (April 15, p. 1108) draws attention to this condition, very puzzling in abdominal diagnosis, in which very severe ketosis or pre-coma sometimes produces symptoms of acute appendicitis, an ulcer perforation, or peritonitis, without any underlying abdominal lesion. It is true, and this is the reason for his letter, that this condition, though well authenticated for years, is not generally known to practitioners nor even to surgeons concerned, as was shown by the last case I met. An experienced and well-known abdominal surgeon telephoned me at 3 a.m. saying he had to operate at once for a classical acute appendix in a diabetic boy patient of 9 and would I come to advise on the insulin treatment before and after operation. On inquiry he said the glycosuria was very heavy ; but made no mention of the ketonuria. When I hurried along the smell of acetone suggested the diagnosis before the chemical test confirmed it. I think the surgeon at first doubted my opinion, as he had never heard of the condition. However, insulin and saline treatment removed the ketosis and the pain *pari passu* and the operation was cancelled.

I have searched one up-to-date and very popular students' surgical textbook for any mention of this abdominal emergency and found none: if all surgical textbooks (perhaps some do) included it under "Acute Abdomen" and indexed it, general ignorance would soon be dispelled and many lives saved.—I am, etc.,

London W.1. R. D. LAWRENCE.

SIR,—"Sometimes, inexplicably, there is abdominal pain or, more frequently, vomiting. Hence diabetic ketosis is important in the differential diagnosis of the acute abdomen."[1] I have quoted this verbatim from what is probably the most popular textbook on medicine to-day, so that if, as Dr. P. Edward Dipple suggests (April 15, p. 1108), students and practitioners are unaware of its existence it is simply due to their limited reading.

As a medical student I was aware of the "acute diabetic abdomen," but regarded it as somewhat of a rarity. However, during the course of a year's casualty experience, I saw five cases of diabetic pre-coma present as acute abdomens: all were admitted to medical wards with the correct diagnosis. At the hospitals where I have worked all acute cases passed through the casualty department. Before the casualty officer sees the patient, the nurses have done a "T.P.R." and urinalysis. Since the urine of a patient in diabetic pre-coma invariably contains ketone bodies and sugar, the nurse could write the diagnosis on the notes before the doctor even sees the patient. For this reason the diagnosis was never missed and no delay in instituting treatment occurred.

The detection of diabetes is, surely, the reason *par excellence* why the urine of every patient should be tested routinely. I am sure no further cases of diabetes would be seen in the surgical wards of the Royal Gwent Hospital if this basic regime were to be adopted.—I am, etc.,

London S.E.1. K. LANCER.

REFERENCE

[1] *The Principles and Practice of Medicine*, 2nd edition, 1954, edited by S. Davidson, Livingstone, Edinburgh.

Treatment of Alcoholism

SIR,—As shown in your report (March 18, p. 818), Dr. J. J. Crawshaw in his paper read at the Joint B.M.A. Annual Meeting in Auckland managed to discuss a great many aspects of alcoholism. The estimated number of chronic alcoholics in New Zealand of between 15,000 and 20,000 is far below any estimate of the number in this country, but, whereas New Zealand has provided a hostel for alcoholics seeking employment and an "inebriates' island" which alcoholics can enter voluntarily or on court order, there is no special alcoholic hostel in this country.

Alcoholics did not fit readily into an ordinary day hospital,[1] a rehabilitation centre for aggressive or inadequate personalities,[2] a hostel for homeless offenders,[3] or a common lodging-house,[4] just as the ordinary mental hospital does not seem to be a suitable place for them.[5 6] On the other hand, alcoholics seem to feel much more at home in therapeutic communities formed exclusively (or predominantly) by alcoholics, and just as they are generally very co-operative in special alcoholic units[7] they may fit in quite well in special alcoholic hostels. There certainly seems to be a need and a case for the establishment of a few experimental hostels and half-way houses—day and night hospitals for discharged hospital patients or for alcoholics who still have got homes and families or are able to keep at work, and special hostels for the down-and-outs and ex-prisoners or chronic drunkenness offenders,[8] etc. The work of such hostels should be integrated with that of out-patient clinics and regional in-patient units[7 9] so as to take care of alcoholics of all types and of all strata of society.

Dr. Crawshaw stated that the alcoholic's co-operation was a *sine qua non* of successful treatment: "The patient must have resolved to avoid alcohol completely." This seems certainly true, but with the proviso that the alcoholic has not necessarily to be in a co-operative frame of mind when treatment is started. If at the end of his hospital stay the alcoholic is still full of self-pity, resentment, and "righteous indignation" and if he then still feels he can drink in moderation, the outlook is naturally hopeless. But an initially uncooperative, cynical, and resentful attitude may sometimes change if the alcoholic is treated within the framework of an alcoholic community. At St. Bernard's Hospital (female) alcoholics sent along from the courts without condition of residence often discharged themselves after a few days—indeed as soon as it dawned on them that they were not legally compelled to stay—but those with a condition of residence, though initially resentful or openly hostile, often became quite co-operative once they had stayed long enough for "exposure" to take. The question of compulsory detention and treatment of alcoholics—under certain circumstances—brought up at the New Zealand Meeting, as it was a few months ago in your correspondence columns,[10 11] seems to merit serious consideration.

Discussing the treatment of alcoholics, Dr. Crawshaw rightly suggested that barbiturates and paraldehyde

should be avoided. Non-barbiturate hypnotics on the whole seem to carry a much lesser risk of habit-formation and addiction, though in the case of unstable alcoholics such a happening can never be excluded. Among the non-barbiturate hypnotics methyprylone, glutethimide, and the newer thalidomide ("distaval") and methaqualone hydrochloride ("melsedin") have so far in our experience proved quite suitable for alcoholics. In the case of thalidomide, the possibility of peripheral neuropathy as a toxic manifestation[12–14] must be kept in mind, but several of our patients with evidence of alcoholic neuropathy showed a satisfactory response to treatment though receiving thalidomide, as in the case recently reported by Shafar.[14]—I am, etc.,

M. M. GLATT.

St. Bernard's Hospital,
Southall, Middlesex.

REFERENCES

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2 Maxwell Jones, personal communication.
3 Turner, M., *Med. World*, 1959, **90**, 63.
4 —— *Forgotten Men*, 1960. National Council of Social Service, London.
5 Atkin, I., *Brit. med. J.*, 1959, **1**, 293.
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14 Shafar, J., ibid., 1961, **1**, 829.

Resurgence of V.D.

SIR,—Undoubtedly the most disturbing feature of the present rise in incidence of venereal disease is the youth of many of the patients seen in our clinics, and there seems little doubt that sexual promiscuity is rife throughout the country. This, together with ignorance of its dangers, is a situation calling for the most urgent education of the youth of our country. Twenty or so years ago a campaign of education in such matters was vigorously carried out, but after the war, when so many people looked upon the venereal diseases as dying diseases, it practically ceased. We thus have a new generation who are almost totally ignorant of the dangers they are running, and intensive propaganda is urgently necessary.

The extent of the problem may, perhaps, be better understood if the following figures are closely studied. They are the actual figures of attendances at two male and two female venereal disease clinics (or special treatment centres) in the City of Liverpool. There is no reason to suppose that they differ widely from other large centres of population.

Number of New Cases Reporting at the Clinics During 1960, *in Age Groups*

Males		Females	
Age	No. of Patients	Age	No. of Patients
		11	1
		12	1
		13	10
14	1	14	21
15	3	15	58
16	47	16	63
17	83	17	56
18	121	18	92
19	216	19	86
20	275	20	68
21	328	21	100
22	388	22	74
23	409	23	62
24	432	24	54
25	527	25	40
Over 25	2,639	Over 25	251

These are truly appalling figures and show that in the case of male patients there were 471 teenagers between the ages of 14 and 19, a total of 8.6% of all attendances. If we include all patients between 14 and 24 the figure rises to 2,830, or 51.7% of all attendances. In the case of female patients we find that there were 388 teenagers between the ages of 11 and 19, a total of 37.4% of all attendances. If we include all patients between 11 and 25 the figure rises to 786, or 75.8% of all attendances. Such figures must give us all food for thought. The extreme youth of many of the female patients surely suggests lack of parental control and instruction, and quite obviously calls for urgent action. We cannot afford to be complacent in the face of such a state of affairs. It must be borne in mind that the figures given in no way delimit the amount of promiscuity in the country, they only apply to those who are infected with venereal disease or who believe themselves to be infected. Many, one must assume, never report to the clinics. Terrible as these figures are, they are not the whole story, since, with the advent of antibiotics, many patients never report to the clinics but are seen and treated either privately or by their own general practitioners, from whom no statistics are obtained.

An attempt has been made to show that promiscuity is a very serious problem in the teenager as well as in young people in the early twenties, and that such patients are responsible for many venereal infections. It is stressed that many of the patients were, on examination, found to be clear of venereal disease, but, nevertheless, all had taken the risk of being so infected. It is a particularly unpalatable fact that so many of the females were of very tender years, and the problem calls for very serious investigation, education, and publicity. The figures given apply only to Liverpool, but a fuller report on the country as a whole has been published by the British Co-operative Clinical Group.[1]—I am, etc.,

E. E. PREBBLE.

Special Clinic,
Liverpool Royal Infirmary,
Liverpool 3.

REFERENCE

1 British Co-operative Clinical Group, *Brit. J. vener. Dis.*, 1960, **36**, 216.

Wassermann Test in Pregnancy

SIR,—I wish to make a plea for routine testing of Wassermann reaction in *all* pregnant women, not primigravidae only. I have seen three positive results in multigravidae in the past four weeks, and in one of them I know that the test was negative in the previous pregnancy.

Routine haemoglobin estimation and checking of the Rh factor is done conscientiously by general practitioners, but there is a dangerous tendency to believe that Wassermann tests are unnecessary. The laboratory technicians willingly take blood for Wassermann tests at the same time as for the haemoglobin, but can do so only at the doctor's request.—I am, etc.,

MARGARET W. BLACKWOOD.

Public Health Department,
Barnsley, Yorks.

Venereophobia

SIR,—I have been interested in the correspondence on this matter (January 21, p. 206, and February 18, p. 507) and have a case of my own to contribute to the collection.

The patient was a senior N.C.O. in the regular army, and while stationed in Japan after the war he spent one night with a Japanese prostitute and immediately became so filled

with remorse and guilt, not to mention fear of having contracted V.D., that he underwent complete investigation and had a course of prophylactic penicillin. He was told that he was free from infection but was not convinced, and even after repeatedly negative W.R.s, etc., his obsession became stronger and he was eventually invalided home to this country on psychiatric grounds. He came to see me about it and I had his W.R. done again, but yet another negative result failed to convince him of his freedom from infection, and a few days afterwards he committed suicide by hanging himself in a neighbour's garage, leaving his wife and two young sons to fend for themselves.

—I am, etc.,

Auckland, New Zealand. D. C. FAULL.

Prognosis in Schizophrenia

SIR,—Dr. Henry R. Rollin's letter (April 15, p. 1104) must make disheartening reading to anyone with insufficient knowledge of the effect of modern drugs on schizophrenic states. Some of your correspondent's conclusions appear to be based on the premise that modern methods of treatment (of schizophrenia) can do nothing more than expedite the advent of a remission. Dr. Rollin argues that modern methods of treatment do not prevent recurrences, and, in support of this contention, submits that the number of readmissions must represent an alarming number of relapses. Unlike Dr. Rollin, I have been impressed by the efficacy of the phenothiazine group of drugs in controlling and suppressing schizophrenic symptoms. In my experience, relapses are exceptional in those numerous cases of schizophrenia in which a prompt and adequate remission has followed the use of one or other of the phenothiazine drugs, *provided* the patient continues to take the appropriate drug conscientiously and in accordance with instructions. To be sure, a steady trickle of patients who responded well initially to phenothiazine medication have to be readmitted, but the majority of these frankly confess that they have ceased to take their tablets. A high proportion of those patients who respond favourably to tranquillizing drugs are destined to become useful members of society, and to work competently in the home, office, or factory. Indeed, so potent are these modern drugs in controlling the manifestations of schizophrenia that selected cases can be treated from first to last as out-patients.

Unhappily, not every schizophrenic shows a favourable response to drugs, long-standing cases being especially refractory to their influence. It is these patients whose schizophrenic symptoms cannot be satisfactorily controlled by treatment, or who have travelled too far along the road to dementia, who need to remain within the confines of a psychiatric hospital. In my view, it is wrong to allow patients to leave hospital who are not only not well enough to do so but who are burdened with the additional handicap of having no home, no job, and no family to which they can repair. I have no doubt that a significant number of such people would (as Dr. Rollin suggests) find their way to prison, the doss-house, or the embankment, should they be discharged from hospital with no visible means of succour or support. The fact that Dr. Rollin has examined in prison over a period of months no less than 17 seriously disturbed schizophrenics, all of whom were former patients of psychiatric hospitals, does suggest that the admission of patients to psychiatric hospitals on an *informal* basis has been somewhat overdone. The root of the trouble lies, I suspect, in the activities of those "forward-looking" psychiatrists who tend to think in terms of the maximum, rather than the *optimum*, number of open wards and informal patients. It would be tragic if recent hard-won gains in the guise of increased freedom for the inmates of psychiatric hospitals were to be jeopardized by incautious thinking of the kind mentioned above, for public opinion—ever fickle—could soon grow hostile to any system which failed to protect the community from dangerous patients, or patients from the dangers of the community.

—I am, etc.,

Ilkley, Yorks. J. TODD.

Routine Lumbar Radiography

SIR,—In his letter (April 15, p. 1106) Mr. D. J. Reid suggests that for patients complaining of back pain an adequate diagnosis can be made without routine radiological examination. This is a courageous statement and a most attractive proposition in many ways, and its implementation throughout our out-patient departments, especially in the orthopaedic and physical medicine clinics, would doubtless result in considerable economy and saving of time, but surely at the expense of lowering an acceptable clinical standard. Many patients suffering from backache, with the exception of those with obvious evidence of prolapsed intervertebral disk, are referred for the purpose of eliminating the presence of serious disease. However thorough the clinical examination, it cannot be denied that radiological investigation is a very helpful adjunct.

Osteoporosis, vertebral haemangioma, Paget's disease, and osteochondritis need give no specific clinical signs and no increase in the sedimentation rate, which is suggested as a cheap alternative, but many of these conditions might be harmfully treated by manipulation. A full clinical examination very often fails to reveal the primary focus of a spinal metastasis. In mechanical derangements of the lumbar spine radiological examination is of primary assistance in revealing lumbar instability, spondylolisthesis, spondylolysis, or significant disk degeneration. A neoplasm within the spinal canal or an aneurysm anteriorly may give no physical signs but suspicion of the true diagnosis be aroused by a routine film. In the early stages of many other comparatively serious conditions such as tuberculosis, low-grade osteomyelitis, ankylosing spondylitis, and myelomatosis clinical signs may be minimal but *x*-ray evidence obvious.

The experienced bone-setter, chiropractor, or osteopath develops a clinical sense which helps him to avoid most of the pitfalls of manipulation, and, recognizing this, the public accept this element of risk wholeheartedly, but to whom should a doctor send a patient for more comprehensive assessment if the consultant is prepared to do the same ?—I am, etc.,

The Middlesex Hospital, London W.1. P. H. NEWMAN.

Surgical Treatment of Parkinsonism

SIR,—I am writing in regard to your leading article (November 12, 1960, p. 1437) concerning the surgical relief of parkinsonism. I am particularly happy to note your interest in this field, and I am very pleased that through the work of Mr. F. J. Gillingham (p. 1395) and others in Great Britain it is becoming apparent that this type of surgical therapy should be made increasingly available to suitably selected patients who suffer from this disease.

Although I find your attention to this matter gratifying, and although I am grateful for your kind reference to my own contributions to this field, I must respectfully call your attention to an inaccuracy in interpretation of my own work, which is worthy of note because it applies to the fundamental concepts of basal ganglia surgery for parkinsonism and other diseases. In your leading article you state, "There can be no justification for magnifying the possible errors by the use of inaccurate apparatus. The use of non-stereotaxic apparatus limits the application of the operation to early and preferably unilateral cases." These statements are somewhat paradoxical, since one would not be willing to use any inaccurate method for early cases and unilateral patients, as these patients deserve at least the same respect and meticulous attention that more advanced cases would require. The subsequent sentence of the leader appears to infer that our own attention has not been directed towards anatomic accuracy. This inference is incorrect.

Although, along with practically everyone else engaged in this type of work, I lay extremely heavy emphasis upon suitable selection of patients for surgery, I do not feel that this type of surgery should be used only in early or unilateral cases. Our own series of 1,800 cases includes patients ranging in age from 8 to 79 years, and varying from early symptomatology to total invalidism. Moreover, although I have stressed that anatomic accuracy by itself will not provide for a successful surgical intervention, nevertheless since 1953 I have been using an apparatus which combines the principles which you refer to as especially safe and accurate. The instrument and technique of operation are described in my monograph on this subject.[1] Since we have operated on more than 1,800 patients with extrapyramidal diseases, with a mortality rate presently less than 2%, and with a follow-up system of observation of patients followed both at our own centre and by a special group from other centres, as described in my monograph, the inference that I would be willing to settle for an inaccurate method of surgery deep within the human brain is one which I could not pass without calling this inaccuracy to your attention.

If I may follow this particular line of thought one step further, I should like to state that you have actually emphasized in your leader precisely the steps which we have stressed which make this type of surgery safe, reasonably certain, and practical for a large group of parkinsonian patients. These steps are: (1) Accurate, but simple, instrumentation combined with accurate *x*-ray localization to provide rapid, reproducible basal-ganglia surgery. (2) Clinical physiologic testing of a surgical lesion deep within the brain, before inflicting a permanent lesion. Because of the fact that parkinsonian patients may demonstrate (*a*) various networks of cortical and subcortical lesions, (*b*) various degrees of ageing of the brain, (*c*) various anatomic variations, and (*d*) varying symptomatology, it is absolutely necessary to realize that from time to time the lesion must be varied to suit a particular patient. For this reason some type of physiologic testing of the lesion site is necessary. We prefer the method of balloon inflation which we describe. However, others have other reliable methods which are useful and practical. It is only the principle of clinical physiologic testing which I wish to stress, not necessarily the method for its production. (3) The importance of permitting a cannula to remain within the brain to produce gradual destruction over a period of time so that this lesion may be checked roentgenographically as well as clinico-physiologically during its production has been one of the cornerstones of this type of surgery so far as I personally am concerned.

Thus, although anatomic accuracy in this type of surgery is obviously of the utmost importance, it is only one of several equally important factors in this particular type of brain surgery. For example, you refer to the fact that accuracy within one millimetre is now possible with various types of instrumentation. However, one must not lose sight of the fact that, even if it were possible to destroy the same cubic millimetre of tissue in each individual human brain, this would not necessarily be desirable because of the anatomic variations, pathologic variations, ageing variations, and other factors which must be taken into account. Moreover, in many instances an electrode with an exposed surface as large as ten millimetres is employed to produce the desirable lesion. Consequently, what must be sought after is practical accuracy which suits the needs of each individual patient. The point which I have tried to make in this regard is that with good three-dimensional roentgenography one can achieve this degree of accuracy with a much simpler type of instrumental approach than has heretofore been generally believed to be the case. As a corollary to this simplification of approach, I might add that this is what has made it possible to apply basal-ganglia surgery to the aged and to the far-advanced case as well as to the earlier and unilateral case. The aged and incapacitated patient cannot tolerate long, tedious, complicated procedures. It is for that reason that the simplified but practically accurate approach which you advocate in your editorial is so important. It is precisely this type of approach which I have advocated, which does not appear to be apparent in your editorial.

I have sought by careful documentation, such as that presented in the monograph, to provide a firm, scientific basis for the support of these principles. Purely anatomic stereotaxis is too stereotyped. Certainly anatomic accuracy, clinico-physiologic testing, and gradual infliction of the lesion are basic fundamental concepts to be applied to this type of surgery. However, on the basis of our own experience, I would emphasize as well that careful selection of candidates for surgery, including both early and advanced cases, is as important as meticulous surgical technique.—I am, etc.,

Division of Neuromuscular Diseases, New York University School of Medicine, New York.
IRVING S. COOPER.

REFERENCE

[1] Cooper, I. S., *Parkinsonism: Its Medical and Surgical Therapy*, 1961. Charles C. Thomas, Illinois.

Waste of Medical Manpower

SIR,—Once again my *B.M.J.*—the issue for February 11 with Sir Douglas Robb's Presidential Address (p. 375)—has reached me full of articles encouraging men to help the underdeveloped countries.

I would first like to agree whole-heartedly that there are many parts of the world, such as the one in which I am now living, where doctors are desperately needed. My husband, who works in the Agricultural Department, and I are stationed in a division of 10,000 square miles, with a population of a quarter of a million people, whose only hospital is separated from the majority of its people by the River Benue, which is in spate, and therefore unnavigable by local transport, for about six months of the year. The only hospital within our reach is 100 miles away by bumpy dirt road, which is liable to be cut by the rains. There are nine dispensaries in the area, of which four are, at present, staffed by "trained dispensary attendants"; there is, of course, no doctor this side of the river. The only ambulance broke down six months ago and has not been repaired.

Until I married in June last year, I had been working as an obstetric registrar in a London teaching hospital, and as soon as I arrived here I applied for employment. Six months later I was put on the register. Eight months later I was told second-hand that "it was considered a waste to employ a temporary doctor on a month-to-month basis away from a hospital." It seems

to me that it is far more of a waste not to employ a doctor who is already on the spot and who does not ask for a high salary, air fares, compensation, or pension. Needless to say, there is no shortage of work, particularly in my own field of obstetrics, and I have brought much of the necessary equipment with me from England.

Sir Douglas Robb says: "In certain parts it is quite a struggle for a doctor to get medical work to do. . . . In other parts there are large numbers of human beings with little or no prospect of service. . . ." Unfortunately, in my area, both these things are true and there seems to be no chance of remedying them. Although there is a desperate shortage of medical staff, mine is by no means the only case in Nigeria alone where there has been a qualified doctor who is anxious to help and who has received no encouragement at all. Let these underdeveloped countries make use of the facilities at hand before they expend large sums of money in inducing more men and their families to uproot themselves.—I am, etc.,

Jalingo, Northern Nigeria. P. J. M. WATNEY.

Tendon Transplants

SIR,—In your leading article on tendon transplants (April 15, p. 1095) it is regrettable that reference was not made to the condition in which this procedure has so much to offer to so many people. This condition is leprosy, and the estimated leprosy population of the world is about 10 million. The results of the standard procedures of tendon transplant in hand and foot have been spectacular and have brought hope to thousands of patients whose outlook has seemed hopeless.

Many plastic surgeons and orthopaedists in the countries where leprosy is prevalent are trained in this country, and the opportunities opened up by the application of standard procedures in this disease are not appreciated. It is to be hoped that those experienced in this field will have in mind the possibility of visiting leprotic areas in order to demonstrate what can be done. It is no exaggeration to say that at the moment there are many thousands of patients with drop-foot, claw-hand, lagophthalmos, nasal depression, and loss of eyebrows who await only the arrival of someone willing and able to help them, so that not only may they be able to do a job but also be acceptable by a community which is afraid of the recognized deformities associated with leprosy and often will not accept the patient back to his communal life.—I am, etc.,

Solihull Hospital, Birmingham. E. W. PRICE.

Poldine Methosulphate

SIR,—The three interesting papers (April 15, pp. 1066–1080) on this drug confirm earlier observations that poldine suppresses gastric-acid secretion. That it alone is not sufficient for the treatment of duodenal ulcer is surely accepted. In 1958 I wrote,[1] "In this way it (poldine) differs strikingly from atropine. Furthermore, the alkaline non-parietal secretions of the gastric mucosa which have a protective action are not reduced by it. The reduction of acid volume by the drug makes it much easier to obtain more prolonged influence from alkali administration as a single night-dose or as slowly dissolving tablets in the daytime," and this is still the method of choice. It is most important that the alkaline tablet should be one which has been proved by clinical tests to disintegrate in the mouth at the right speed to procure effective acid control, at not more than two tablets hourly.—I am, etc.,

London W.1. A. H. DOUTHWAITE.

REFERENCE

[1] Douthwaite, A. H., *Proc. roy. Soc. Med.*, 1958, **51**, 1063.

Vagotomy for Peptic Ulcer

SIR,—Recent correspondence shows some difference of opinion regarding the importance of diarrhoea as a complication of vagotomy and gastroenterostomy. Mr. R. L. Holt (March 18, p. 824) considers that the incidence is no greater than after partial gastrectomy, and it is interesting to note that he has had no troublesome cases of this complication in a large series. This, unfortunately, has not been my experience, and I think some pertinent details might be given.

N. J. Logie and I (unpublished observations) found that in 331 patients followed up 5–15 years after Polya partial gastrectomy, 20.5% suffered from intermittent diarrhoea. In 43 cases this was little or no disability and consisted of passing three to five loose stools a day for one to three days, the attacks occurring two or three times a year. In 20 cases attacks occurred every six to twelve weeks, and this was classed as a moderate disability. In five severe cases diarrhoeal attacks occurred every two to five weeks and were often incapacitating. Two patients were required to change their occupation on this account.

Many patients will not volunteer information about an altered bowel habit following gastric surgery. Since I became aware of the incidence of diarrhoea after operations for duodenal ulcer I have been careful to keep a record of the patient's bowel habit prior to operation. About 60% of patients followed up within three months of surgery for peptic ulcer have experienced an episode of diarrhoea since the operation. The significance of this is doubtful, but some importance can be attached to the incidence of recurrent episodes of diarrhoea in patients followed up for longer periods. Tables I and II show details of altered bowel habit in 144 patients followed up six months to two years after partial gastrectomy or vagotomy and gastroenterostomy, and in no case was diarrhoea noted before operation. In addition, 17 patients were seen who had been treated by vagotomy for anastomotic ulcer following partial gastrectomy, and in only one of them had diarrhoea followed the gastric resection.

TABLE I.—*Incidence of Diarrhoea After Gastric Operations*

	Total No.	No Alteration in Bowel Habit	Intermittent Diarrhoea
Vagotomy and gastroenterostomy ..	67	42	15 (22%)
Polya partial gastrectomy	77	67	10 (13%)
Anastomotic ulcer treated by vagotomy	17	10	7 (41%)

TABLE II.—*Severity of Diarrhoea After Gastric Operations*

	No.	Mild	Moderate	Severe
Vagotomy and gastroenterostomy	15	7	5	3
Polya partial gastrectomy ..	10	8	2	—
Vagotomy for anastomotic ulcer ..	7	2	3	2

These results suggest that intermittent diarrhoea is a complication of both partial gastrectomy and vagotomy and gastroenterostomy. It is significant that the severe cases are associated with vagotomy, and in these patients it represents a serious disability. If the cause of diarrhoea in all patients is acute enterocolitis, as suggested by Mr. Holt, then it seems clear that vagotomy makes some patients particularly susceptible to this affliction. Burge and Clark[1] suggest that

diarrhoea after vagotomy is due to denervation of the coeliac plexus and interruption of the parasympathetic nerves to the pancreas. The experimental evidence of changes in the function of the pancreas after parasympathetic denervation is conflicting. Mitchell[2] states that the coeliac branch of the posterior vagus nerve contains parasympathetic fibres distributed to most of the abdominal viscera except the stomach and liver, and the preservation of intestinal innervation may be as important as preserving the extrinsic nerve supply to the pancreas. Burge's selective vagotomy is a logical approach to the treatment of duodenal ulcer, and his early results show that diarrhoea has not occurred after this operation. If these findings can be confirmed, then vagotomy and gastroenterostomy is rid of one of its worst complications. There is only one possible objection to this procedure which should be considered.

Regeneration of the vagus nerves does not occur after ligation and division. Murray and Thompson[3] have shown, however, that, if a nerve is incompletely divided, collateral nerve sprouting can occur from the remaining undivided nerve fibres, and these nerve sprouts can, in certain circumstances, re-establish communications with the partially denervated organ, allowing full recovery of function after a suitable period. It is theoretically possible that selective vagotomy might allow this phenomenon to occur, and this possibility is at present being investigated by animal experiment. The Burge and Vane[4] test for complete vagotomy is certainly a time-consuming procedure, but, since it is the only test available which can be used to verify complete neurectomy at the time of operation, it is infinitely preferable to a post-operative insulin test-meal. The reliability of Burge's test is dependent upon the care with which it is performed. I have found it particularly useful in those cases where there are multiple nerve trunks. I have also seen the test detect undivided vagal nerves after a competent gastric surgeon has performed what he considered to be a complete vagotomy. Burge and Vane have given us a useful tool which, if correctly applied, will help many surgeons to perform a complete vagotomy. If selective vagotomy is proved to be free from the complication of diarrhoea, and satisfactory in other respects, another important step has been taken.—I am, etc.,

The Royal Infirmary, Aberdeen. CHARLES G. CLARK.

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2 Mitchell, G. A. G., *Anatomy of the Autonomic Nervous System*, 1953, p. 187. E. and S. Livingstone, Edinburgh.
3 Murray, J. G., and Thompson, J. W., *Brit. med. Bull.*, 1957, **13**, 213.
4 Burge, H., and Vane, J. R., *Brit. med. J.*, 1958, **1**, 615.

Accident Neurosis

SIR,—Dr. Henry Miller deserves the heartfelt thanks of all doctors who are concerned with trauma for his excellent investigation of the so-called accident neurosis syndrome. His Milroy Lectures (April 1, p. 919, and April 8, p. 992) should lend courage to the convictions of many general practitioners and surgeons and thereby reduce considerably the pressure on their consulting-rooms and clinics.

Dr. Miller asks: "Why do only a third of those involved in minor accidents succumb to accident neurosis?" The answer might be that only one-third of this group are dishonest. It would be cynical to suggest that this is an unexpectedly low proportion.

In every case in his series Dr. Miller found that there was "an absolute failure to respond to therapy until the compensation issue was settled, after which nearly all the cases described recovered completely without treatment." Dr. Miller is the first to produce convincing statistical evidence of the truth of these assertions. His lectures confirm my belief that the condition would be more correctly termed the avaricious neuritis syndrome.—I am, etc.,

Birmingham 15. J. A. RYAN.

Menstrual Red Eye

SIR,—As menstrual red eye can be unilateral (Mr. M. D. O'Brien, February 4, p. 359; Mr. Robert W. Stephenson, Dr. Peter M. Green, March 4, p. 673), and is not "physiological," obviously something besides physiological premenstrual water retention is involved. The writer has seen, for instance, (i) a painful, injected episcleritis of over two months' standing in a female that only subsided following cauterization of a small linear erosion on the anterior wall of the ipsilateral auditory canal; (ii) a recurring injection and itching of the inner canthus of the left eye in a male, which could be evoked, subdued, and permanently banished by 70% alcohol, cocaine, and pure phenol applied in that order to a small fissure at the apex of the ipsilateral nostril; (iii) a male in whom cold water splashed on the eyes on rinsing would produce a diffusely red right eye: an ephedrine-soaked swab placed between the right middle turbinate and the septum would do likewise, but not a cold, alcohol-soaked swab applied in turn to the right cheek, nose, forehead, and auditory canal; and (iv) males and females in whom ocular redness, injection, and lacrimation has followed stimulation of microscopic lesions of the ipsilateral cheek or nose with 70% alcohol. As far as the raised intraocular pressure is concerned there is much clinical and experimental evidence to suggest that this is controlled by the central (diencephalon) and peripheral nervous systems (3rd, 5th, and 7th cranial nerves, and cervical sympathetic).[1]

As premenstrual engorgement of the nasal mucous membrane is a regular physiological event it is not improbable that pressure(distension)-evoked axonal reflexes from micro- and macro-scopic lesions in this and the related 5th-nerve territory are the *raison d'être* for menstrual red eye. A well-timed monthly diuresis may give these patients relief, but to say that such cases are due to water retention is insufficient for truth.—I am, etc.,

Capetown. M. GLASS.

REFERENCE

1 *Brit. med. J.*, 1958, **1**, 387.

Night Alarm and Phenelzine

SIR,—Two of my female out-patients, taking moderately high doses of "nardil" (phenelzine), have complained of a dramatic symptom which I have not seen reported. I believe it to be a side-effect of the drug, but I can see that, in a hysterical or delusional patient, the symptom might be discounted. Minor variants have been experienced by other patients. Both patients complained of being suddenly jerked wide awake in the night, one "as if by an electric shock" and the other "by a flash of light as if I had been hit on the head." The accompanying emotion was one of great alarm, and the experience was repeated until the dosage of phenelzine was reduced or the evening dose omitted.

Every mental hospital psychiatrist has been accused of giving surreptitious electrical treatment in the night. Phenelzine may provide a basis for such an idea. This drug not only elevates mood but also, it seems (in an electrifying manner), sometimes the patient herself.—I am, etc.,

Dingleton Hospital, Melrose, Roxburghshire. J. K. W. MORRICE.

Marking the Skin

SIR,—While admiring the ingenuity of my colleague, Mr. Michael Reilly (April 1, p. 971), I prefer a method less apt to arouse apprehension in the nervous female. I use a cellulose cement—for example, "durofix"—obtainable in bottles, coloured with gentian violet. If the grease is removed from the skin a dab of this cement often needs peeling off with the knife. I stumbled on this idea by noticing how the cement stuck to my fingers after mending household china.—I am, etc.,

Yelverton, Devon. EDRIC WILSON.

SIR,—I note that Mr. Michael Reilly (April 1, p. 971) asks "what simple genius" thought of marking the skin with a needle prior to varicose-vein operations. I saw this method used in a clinic in Italy fifteen years ago, and was not impressed. I felt that the patient prior to operation had quite enough anxiety without adding to it. The pen that I have described in my letter (March 18, p. 830) is, in my opinion, the most satisfactory and kindly method.—I am, etc.,

London W.1. R. ROWDEN FOOTE.

Prevention of Dental Caries

SIR,—Dr. F. D. F. Steede's letter (March 11, p. 749) suggests it is unreasonable to await the results of the present fluoridation studies. Surely this is a necessary precaution, since the foundations upon which the various advisory bodies are likely to have based their opinion have been adversely criticized quite recently by Sutton.[1] The findings of Nómmik[2] undermine confidence in the ability of fluoridated water to reduce the incidence of dental caries in every community.

If prevention means no more new cavities, then modification of diet appears to be the only method so far shown to be successful.[3,4] Two paragraphs from the latter paper read as follows:

"The work has proved that the combined efforts of the dental surgeon and the dietitian are vastly more effective than the sum total of their individual approaches. The dietetic advice given to assist in arresting caries has also resulted in general benefit to the child. The weighing and measuring develop in the parent a broader interest in the child's health, which is more effective than a request for preventive measures of a purely dental nature. Fretful, ill-disciplined children with disgusting mouths have changed into happy co-operative patients with clean mouths and teeth showing arrested caries. Gross caries can be regarded as a diagnostic index of dietetic imbalance (and probably unsatisfactory nutrition).

"Students responsible for the dental care of the children are able to appreciate, from the evidence among their own patients, that caries can be controlled by reasonable attention to diet. They also begin to understand more fully that the teeth are truly part of the biological whole person."

May I suggest that Dr. Steede and others occupy themselves during the period of impatient waiting vigorously implementing the four conclusions on p. 26 of the *Memorandum on the Dental Health of Children*,[5] and at the same time test the effect of a combined attack on some of his caries cases, including one or two overweight children? Send them to a dietitian for assessment and appropriate diet modification. He should in this way solve two of the school medical officer's problems.—I am, etc.,

Coventry. S. P. MEACOCK.

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1. Sutton, P. R. N., *Fluoridation; Errors and Omissions in Experimental Trials*, 1959. Cambridge Univ. Press, London.
2. Nómmik, H., *Fluorine in Swedish Agriculture Products, Soil and Drinking Water*, 1953. Almqvist, Stockholm.
3. Price-Weston, A., *Nutrition and Physical Degeneration*, 1939, pp. 288–290. Hoeber, New York.
4. Horsnell, A. A., and Scott, E., *Proc. Nutr. Soc.*, 1959, **18**, 91.
5. British Dental Association, *Memorandum on Dental Health of Children*, 1959. British Dental Association, London.

Cigarette in the Mouth

SIR,—The letter from Dr. Gwilym Evans (April 1, p. 971) presents an all-too-familiar picture. The man who has a cigarette in his mouth when he goes out in the morning and still has one when he comes back in the evening is always a likely candidate for carcinoma of the lung, and it is difficult to believe that a heavy smoker of this type does not inhale the cigarette smoke. The fact that pipe-smokers and cigar-smokers, who do not inhale, are much less liable to carcinoma of the bronchus is supporting evidence of this statement.

I think, in fact, the particular pattern shown here, and common amongst a lot of occupations, including that of a barber, is the intermittent smoker who stubs out his cigarettes and re-lights them. I have observed that barbers who are heavy cigarette-smokers frequently light a cigarette between each haircut, have a few puffs, stub it out, and even at times re-light it for a few more puffs in the course of a haircut. There is some evidence that this method of smoking a cigarette increases the amount of carcinogen absorbed, and, certainly, my own barber, who practised this to my knowledge for many years, duly arrived for surgery for his carcinoma of bronchus. This may, in fact, be one of the mechanisms for the familiar triad of clubbed brown fingers, an upper abdominal scar resulting from an operation for peptic ulcer, and an *x*-ray of the chest showing an opacity in the lung. Dr. Gwilym Evans's suggestion that merely burning a cigarette between the lips is likely to give rise to carcinoma of the bronchus would be against all common sense in scientific medicine.—I am, etc.,

Liverpool Thoracic Surgical Centre, Liverpool 14. LESLIE J. TEMPLE.

Bilateral Ectopic Pregnancy

SIR,—In view of the rarity of bilateral ectopic pregnancies, I should like to report a case of ectopic pregnancy in both fallopian tubes, at an interval of 19 years between each pregnancy, in a nullipara.

The patient is of Ukrainian stock, and was 21 years old in 1941, when she became pregnant soon after marriage. She was about two and a half to three months pregnant when she had a ruptured ectopic pregnancy of the right fallopian tube, which nearly ended catastrophically, as she had to travel a distance of over 40 miles to have the necessary surgery done, with blood transfusions. She remained nulliparous until October, 1960, when she came to see me regarding pains and cramps in her lower abdomen. Her last menstrual period was August 1. In September she had some "spotting" per vaginam. On October 14, upon examination, I suspected an ectopic pregnancy in the left fallopian tube, and advised her accordingly, suggesting that she should go into hospital and have a laparotomy, if a

sudden attack of pain occurred. On October 29, she reported that she felt something was going to rupture. I advised an immediate laparotomy, and found an ectopic pregnancy in the left fallopian tube, consistent with her period of pregnancy. Her age was 41 years on this occasion, and she made an uninterrupted recovery.

—I am, etc.,

Winnipegosis, Manitoba, Canada. A. H. BARTLEY.

Reiter's Disease

SIR,—I am sorry to disagree with Dr. J. H. Baron (February 11, p. 426), who has kindly referred to my suggestion in 1958[1] that Hippocrates was the first to describe Reiter's disease. My view that Aphorism 30 refers to a specific act of intercourse and not to an "age group" is supported by Ruiz Moreno, the Argentinian scholar-rheumatologist. He has thus translated the aphorism into Spanish: "Un joven no tiene gota ante del uso del coito."[2] Ruiz Moreno says Hippocrates regarded podagra as punishment for intemperance; women were relatively (not absolutely) immune because they had more temperate habits.

In my previous letter[1] I mentioned, but had not seen, Musgrave's *De Arthritide Symptomatica*.[3] Now I have a copy of this remarkable work which clearly describes the arthritides that follow urethritis (venereal and non-venereal), dermatitis, colitis, and other internal diseases. It would certainly repay translation into English.—I am, etc.,

Institute of Rheumatology, East Melbourne, Victoria, Australia. MICHAEL KELLY.

REFERENCES

[1] *Brit. med. J.*, 1958, **2**, 449.
[2] Ruiz Moreno, A., *Las Afecciones Reumaticas en la Corpus hippocraticum*, 1941, p. 22. Castagnole, Buenos Aires.
[3] Musgrave, Guilhelmus, *De Arthritide Symptomatica Dissertatio*, 1703, p. 251. Yeo and Bishop, London.

Cholestatic Hepatitis

SIR,—In your annotation on cholestatic hepatitis (April 8, p. 1023) you offer a mechanical explanation for the observed inverse relationship between the severity of cell damage and the occurrence of biliary stasis. This view would seem to be confirmed by consideration of drug-induced jaundice, hepatic histology, and prognosis. Thus the outlook is much worse in the hepatocellular jaundice of iproniazid as compared with the biliary stasis associated, for example, with chlorpromazine.—I am, etc.,

Law Hospital, Carluke, Lanarkshire. J. R. MACKENZIE.

Lavatory Seats

SIR,—Dr. Yolande Friedl's letter (April 1, p. 968) is timely because our public lavatory hygiene generally still leaves much room for improvement. We often fail to put first things first. For example, local authorities may prosecute dairies and other food firms for harmless foreign bodies in milk bottles or other packaged foods which, being sterile, present no public health hazard at all,[1] and yet give no facilities for hand-washing in public lavatories after defaecation. It is only recently that wash basins have made their appearance in some public lavatories, and there are still many without washing facilities.

The usual wooden lavatory seat is hygienically a menace, and the split seat made of plastic or other easily cleansable[2] material should be made standard. It is probable that the fresher the contamination the more dangerous it is, and we should do well to bear in mind the saying "A swinging chain denotes a warm seat." The plastic seat may be cold and less comfortable, but it is capable of being maintained in a much safer condition. Wood is impossible to sterilize and difficult to cleanse. Although an attendant may wipe the seat after use with a cloth this does not really cleanse it, and the wiping may merely smear infection from one seat on to another. The unsupported squatting stance for defaecation which is required in some lavatories in France and other countries may be awkward, especially for the old, but it is far more hygienic than the seat method. A lower-sited seat would probably be more hygienic than the type normal in Britain. Such a design coupled with a small basin permitting *immediate* hand-washing should become standard practice in all lavatories.

A further point to bear in mind is that ordinary toilet paper does not prevent contamination of hands by faecal bacteria. One might as well rely on wire netting to hold back mosquitoes. At least three thicknesses are necessary to give adequate protection.[3] The so-called "medication" of toilet paper does not appear to confer any advantage in this respect.—I am, etc.,

London W.1. J. G. DAVIS.

REFERENCES

[1] Davis, J. G., *Med. Offr*, 1958, **100**, 205.
[2] —— *J. Pharm. (Lond.), Suppl.*, 1960, **12**, 29T.
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Electromyographic Changes in Rheumatoid Arthritis

SIR,—Dr. R. A. Yorke draws attention in his letter (March 25, p. 901) to the criteria for the diagnosis of polymyositis. We entirely agree with his observations, and would point out that in the introduction to our paper (March 4, p. 630) we stated these criteria in more or less the same words:

"The electrodiagnostic changes are those of a combination of a primary muscle (myopathic) lesion showing a full interference pattern—small-amplitude broken-up short-duration polyphasic action potentials on the electromyograph—and those of a lower-motor-neurone lesion (denervation)—abnormal intensity-duration curves, and long-duration polyphasic potentials on the electromyogram. The myopathic element usually predominates, and motor-nerve-conduction times are normal, showing that the lesion is at the distal end of the axon."

We felt that there was enough published work on the electrodiagnostic aspects of polymyositis not to demand detailed presentation of our data, but are glad to have this opportunity of amplifying them. In the particular series reported we did not observe any spontaneous activity, but in recent cases we have noted pseudomyotonic discharges and fibrillation in cases where no cause of a neuropathic lesion, such as a carpal tunnel syndrome, coexisted. The average duration of the short-duration action potentials was two milliseconds. The average duration of the long-duration action potentials was 12 milliseconds. In many areas of an affected muscle the picture was entirely made up of very-short-duration polyphasic potentials; in others the proportion of long-duration polyphasics varied from 10 to 50%, but

in most cases half the potentials were long duration, the rest of the potentials being of short duration.

Six of the cases with normal motor conduction times had normal intensity duration curves, the other four had abnormal curves. In all our recent cases of polymyositis of all causes, now numbering more than 30, conduction times have been measured and in all cases have been normal.—We are, etc.,

Department of Physical Medicine, London Hospital, E.1.

V. L. STEINBERG.
C. B. WYNN PARRY.

Medicine Broadcast

SIR,—I do not understand why Mr. W. G. Duncalf says (April 15, p. 1111) that the programmes in the series "Your Life in Their Hands" are not designed to advertise the medical profession. According to the *Concise Oxford Dictionary* an advertisement is a public announcement (usually by placards or in journals). In this case it is by means of television and is certainly a perfectly proper function for the B.B.C. to perform. Whether this is a good thing or a bad thing is quite another matter.—I am, etc.,

London W.1. IAN MACKENZIE.

SIR,—I feel impelled to reply to the taunts of Dr. Rex Binning (April 8, p. 1042), if for no other reason than to associate myself with the witch-doctors and mumbo-jumbo men. It may be, of course, that Dr. Binning is indulging in the "Molière-esque" pastime of baiting the medical profession, in which case I apologize both to him and for him.

It is unfortunate that the essentials of healing are so poorly differentiated in the lay mind. In, say, engineering one would hardly expect one's wrist-watch to be repaired in a marine riveting-shop or to find the casing of an atomic bomb to be turned on a watch-maker's lathe. By all means keep up the surgical programmes for those who enjoy them, but I feel it should be made clear that they demonstrate the skill of the surgical technician and ignore the unmelodramatic work of the general practitioner.

My one regret is that my father should have made so many material sacrifices for my medical education and that I am now instructed in my work by some who have only paid a few of the instalments on their hire-purchase sets. However, in an age of "Do it yourself" and "The customer is always right," I am sure I am not alone in finding comfort in the knowledge that I was taught the Art of Medicine and that *Ars longa, vita brevis est*."—I am, etc.,

Morpeth, Northumberland. G. B. STENHOUSE.

SIR,—I am a clinical student at a London teaching hospital, and was rather disturbed by what a patient of mine told me concerning a surgical technique that was to be carried out on him the following day. The patient was a reasonably intelligent man, married with a grown-up family. He was suffering from a prepyloric ulcer that had failed to respond to prolonged medical treatment, and had been admitted for a partial gastrectomy.

The method he explained to me involved masses of metal piping, weird instruments, and a vast concord of machinery and staff, the operation itself lasting hours and requiring enormous quantities of intravenous blood and fluids. Both he, his family, and friends were quite convinced that if he survived this terrible ordeal it would indeed be a miracle.

On asking him from where he had acquired this vast amount of knowledge, he informed me that he had seen it all on a television programme a year or so ago. He said it was in a "Life in Their Hands" series. Somehow I doubt it. On telling him that the operation entailed nothing of the kind, I was met with blank amazement. It took some time before he believed me. I still do not think the truth dawned on him until after the operation, when he was up and about in a few days, instead of being laid up for weeks as he had honestly believed.

Sir, I am sure that this must occur every day up and down the country in dozens of hospitals, involving many operations and illnesses. I have seen some of these programmes and consider them to be very high-powered. I do not think the poor, gullible public should be blinded with science, and led astray in the manner in which this poor fellow was.—I am, etc.,

Enfield, Middlesex. IAN C. PERRY.

SIR,—No doubt Dr. R. P. W. Kup was being ironical when he suggested in his letter (April 8, p. 1041) that television cameras might visit a crematorium. I write, therefore, to mention that a feature on this subject was in fact included in a "Panorama" broadcast (B.B.C. television) some months ago. All the apparatus was demonstrated, including the pulverizer, which was actually shown in action.

Strangely, the feature did not cause offence. The discussion was serious and unemotional, and the treatment of the subject was clearly not intended as "entertainment." Many people will agree that it is in this spirit of intelligent inquiry that the B.B.C. plan broadcasts of this type.—I am, etc.,

Sully Hospital, Penarth, Glam. W. R. PROBERT.

Rubber Tourniquets in the Home

SIR,—On Wednesday, April 12, on the B.B.C. programme "To-day," the "Radio Doctor" gave advice to the public on what to keep in the home for first-aid. I did not agree with many of his opinions, although that is not sufficient reason to write to the *Journal*. But I could not contain myself when he suggested that every home should be equipped with a rubber tourniquet with a buckle.

Tourniquets are not mentioned in *First Aid*, the authorized manual of the St. John Ambulance Association. They have been replaced by a rubber constrictive bandage which should only be applied as a last resort. The recent book, *First Aid in the Factory*, by Lord Taylor[1] condemns both tourniquets and rubber constrictive bandages, saying that they should never be used by any first-aider. To suggest that every home should have one is surely indefensible, and has probably undone a lot of hard work trying to get rid of them. I think such a talk should give a picture of current informed opinion. It might be less colourful, but it would be safe.—I am, etc.,

Bewdley, Worcs. J. GERRARD.

REFERENCE

[1] Taylor, Lord, *First Aid in the Factory, on the Building Site and Farm, in the Shop, Office and Warehouse*, 1960, p. 36. Longmans, London.

Obituary

JULIAN TAYLOR, C.B.E., M.S., F.R.C.S.,
Hon.F.R.A.C.S.

Professor Julian Taylor, consulting surgeon to University College Hospital and the National Hospital, Queen Square, and professor of surgery at the University of Khartum since 1956, died suddenly at his home in Midhurst, Sussex, where he was on leave, on April 15. He was 72 years of age.

Julian Taylor was born on January 26, 1889, and was educated at University College School and University College Hospital. He qualified in 1911, graduated M.B., B.S., with honours in medicine, in the following year, and took the F.R.C.S. in 1914. After holding house appointments he became surgical registrar and chief assistant in the surgical unit at his teaching hospital, but on the outbreak of the first world war he joined the R.A.M.C. and served with the 85th Field Ambulance in France and Macedonia. In the early days of his service he was a lance-corporal in the Territorials and was a driver of a heavy horsed ambulance—perhaps the only driver ever to hold the F.R.C.S. Later he was medical officer in charge of a surgical division with 52 and 43 General Hospitals, Salonika. He was appointed O.B.E. in 1919. Continuing his surgical career in London after the war, he proceeded M.S. in 1920 and was elected to the honorary staffs of University College Hospital and the National Hospital, Queen Square. Though he had a special interest in neurological surgery, he remained a general surgeon and was an inspiring and popular teacher at U.C.H. and later at Khartum. He examined in surgery for the Universities of Cambridge, Leeds, and London, was a vice-president of the Royal College of Surgeons, and for long a member of its council, and a former president of the Association of Surgeons and of the Section of Surgery and Neurology of the Royal Society of Medicine.

At the beginning of the second world war he volunteered again for military service and became consulting surgeon, Malaya Command, with the rank of brigadier, A.M.S. He was taken prisoner by the Japanese at the fall of Singapore, and his courageous and unswerving devotion to the welfare of his patients during the terrible years that followed did much to sustain the morale of his fellow prisoners.

Appointed C.B.E. in 1946, he returned to his hospital appointments and private practice in London for a few years before his appointment in 1956 to the chair of surgery in the University of Khartum. He was elected an honorary Fellow of the Royal Australasian College of Surgeons in 1949.

Mr. Taylor married Dr. Edith Margaret Ross-Johnson, who held numerous appointments as an anaesthetist at hospitals in and around London. She died in 1955. They had two sons.

Mr. A. J. GARDHAM writes: May I add a personal tribute to my old friend and colleague Julian Taylor? No one who knew this gallant man could fail to admire him. To love him as we did at U.C.H. it was necessary to live beside him, to understand his moods and his motives, and to share his rather rare intimacies.

Julian was deeply devoted to his hospital, and from the beginning he set out to satisfy his own high standards of what a U.C.H. consultant should be. Long before he himself was firmly established he was seeking merit among his juniors, helping them by every means he could, and urging them on to further achievement. This was a characteristic which lasted all his life and earned him the devotion of a host of juniors as far apart as U.C.H., Singapore, and Khartum. As a very personal note I cherish the memory of the time when Julian and "Snorker" Barrington imposed upon themselves the task of seeing that I obtained my Fellowship. Having achieved their object this magnificent pair of U.C.H. characters proceeded to look after my further education. Julian, in particular, saw to it that when criticism was necessary it was not lacking. As the years went on and the gap between us narrowed we fought some good battles over points on which we did not agree and remained the best of friends.

When war came things were set fair for Julian. Characteristically he jettisoned the lot, and I remember well the moment when he came to tell me that he had decided to do so. What heart-searchings and discussions had gone into it before I never knew, but they must have been considerable. From that time onwards came a series of trials and troubles which might have broken the spirit of any man. Julian simply stuck his chin out a little further each time and forged straight ahead in the rigid code of behaviour which he had set himself. The help that he gave to others by so doing is a story which can best be told by those who were with him in Singapore.

After his retirement from U.C.H. Julian's visits to the hospital were an event which we all enjoyed. He was older and frailer in physique, and a little less outspoken in criticism, but the shrewd, humorous, and kindly eyes remained unchanged, and it did us good to see them. Perhaps the picture I have given is too cold. It should not be, because Julian was a warm, lovable human being with a great zest for the good things of life. These, however, were things to be fitted into the odd moments. Good work well done was his real joy, and he left a fine measure of it behind.

R. S. S. writes: Julian Taylor looked upon himself as primarily a teacher of medical students and young doctors, and there must be many all over the world who owe him gratitude for unbiased and helpful advice about their careers. He did not consider himself an outstanding technician, but in his heyday Julian Taylor was, in the considered opinion of those who knew him best, the soundest surgical opinion in London, though he was opinionated, and made no concessions to please doctors or patients.

A pupil of Wilfred Trotter, Taylor unconsciously imitated that great man in manner, in outlook, and even in walk. Like Trotter, he took all surgery within his ambit, and has been known to do a brain tumour, a gastrectomy, and a tonsillectomy in the same list. He prided himself on his neurosurgery and on his connexion with Queen Square as well as with U.C.H., but as a neurosurgeon he ranked with Trotter and Percy Sargent (who were also general surgeons) rather than with Harvey Cushing and Geoffrey Jefferson, though it was Taylor who, at a critical period in Jefferson's career, persuaded the authorities at Queen Square to put Jefferson on their staff.

Through his unlucky appointment as consulting surgeon to the Malaya Command, Julian Taylor's war service had an adverse effect upon his ambitions. At a time when his contemporaries in other military areas were becoming major-generals and achieving knighthoods, Taylor was a prisoner-of-war in Changi prison camp, struggling with unspeakable conditions and lack of antiseptics and anaesthetics, with 2,500 wounded soldiers, 500 compound fractures, septicaemia, dysentery, avitaminosis, making artificial limbs out of aluminium fan blades and Thomas knee-splints. He tells the heart-rending story, without comment, in Chapter 25 of the volume on "Surgery" in the *History of the Second World War, United Kingdom Medical Services*. When he came back to England from the prison camp his malnutrition was such that he broke both his arms on arrival. Prisoners-of-

war do not greatly commend themselves to higher authority, and Taylor's reward, somewhat delayed, was the C.B.E.—and the admiration of all who knew him.

Mr. AHMED A. YACOUB writes: May I be allowed a note about my revered chief, Professor Julian Taylor, who became professor of surgery in the University of Khartum in 1956? During his term he became the pride of our medical faculty. He loved the Sudan, and became a very sincere friend of the people and the country. Before his time the Sudan had three Sudanese surgeons (Fellows of the Royal College of Surgeons) for its eleven million people. Since September, 1959, Professor Julian Taylor became responsible—with the Ministry of Health—for the training of surgeons. At the time of his death he had twelve who had passed their primary F.R.C.S. either in London or in Khartum, where he had established a training centre two years ago. He trekked to many parts of the Sudan, and saw much more of it than the majority of Sudanese; wherever he went there was a busy operating session in which he dealt with the complicated and difficult surgical cases of the district.

He always stood as a symbol for good relations between peoples—it is largely due to him that the University of Khartum has friendly contacts with our neighbouring countries, Uganda, Nigeria, and Ghana. While he was in the Sudan he attracted two young and competent British surgeons as lecturers in the University of Khartum, and he was hoping to get an orthopaedic surgeon during his vacation. Although he kept reminding us that he was 72 years of age and that his heart was troubling him, his death comes as a shattering and cruel blow, for we loved him dearly.

A memorial service to Mr. Julian Taylor will be held at St. Pancras Church on Wednesday, May 10, at 12 noon.

E. T. D. FLETCHER, M.D., F.R.C.P.

Dr. E. T. D. Fletcher, formerly physician in charge of the department of rheumatism at the Royal Free Hospital, and consulting physician to the Arthur Stanley Institute at the Middlesex Hospital, died in London on April 16. He was 69 years of age.

Ernest Tertius Decimus Fletcher was born in London on October 26, 1891, the son of Professor Banister Fletcher, F.R.I.B.A. Educated at Wellington College, Magdalen College, Cambridge, and St. Bartholomew's Hospital, he graduated M.B., B.Ch. in 1918. For four years before this he had interrupted his medical education by serving as brigade machine-gun officer with the 8th Mounted Brigade, and after qualification he served in the R.A.F. medical service. After holding the post of senior house-physician at St. Bartholomew's he became interested in respiratory diseases, though his first intention was to specialize in orthopaedics and rheumatology. He took the M.R.C.P. in 1927 and became registrar at the Royal Hospital for Diseases of the Chest. Later he was elected to the staff of the Italian Hospital and Queen Mary's Hospital for the East End, and he was physician in charge of the department for respiratory diseases at the St. Marylebone and Western General Dispensary. At this time he published several papers on bronchiectasis and related subjects, and he became editor of the *Postgraduate Medical Journal*.

In 1936 he was appointed assistant physician to the department of physical medicine at the Royal Free Hospital, and from then on he devoted his time to the rheumatic diseases. In 1939 he was Heberden lecturer (on osteo-arthritis) and medallist. During the second world war Dr. Fletcher worked in the Emergency Medical Service, and in 1948 he succeeded Dr. Heald as director of the rheumatological unit at the Royal Free.

Proceeding M.D. in 1943, Dr. Fletcher was elected F.R.C.P. in 1954. He became treasurer of the Heberden Society in 1948, and was its president in 1957. Besides his other hospital appointments he was consulting physician to the Arthur Stanley Institute at the Middlesex Hospital and consultant to the Charterhouse Rheumatism Clinic. In 1953 he was awarded the William Marsden travelling professorship by the Royal Free Hospital, and he visited rheumatism research centres in Europe and America, giving 14 lectures in the U.S.A. His book, *Medical Disorders of the Locomotor System*, was first published in 1946, and went into a second edition five years later.

Dr. Fletcher was twice married, first to Muriel Laver, by whom he had two sons, and secondly, in 1937, to Mary Louise Franks.

C. G. writes: The loss of Ernest Fletcher will be deeply felt by his colleagues in the field of rheumatism, to which he devoted himself with great success during the past 25 years. He was constant in his support of the scientific study of the rheumatic diseases, in encouragement of the young men who passed through his department and who were trained there, and in the organization of research. His textbook was an important contribution.

He was a man of striking personality—elegant and debonair, there was an agreeable touch of the dandy about him. Being witty and light-hearted, he was an excellent companion, with endearing eccentricities. He was not always tactful and was sometimes ruthlessly direct. This occasionally gave offence, but he was in fact an exceedingly kind, loyal, brave, and generous man.

> Fate is a sea without shore, and the soul is a rock that abides,
> But her ears are vexed with the roar, and her face with the foam of the tides.

Courage, and the ability to confront his fate with a proper indifference, were Ernest Fletcher's outstanding characteristics. He accepted stoically the death of his younger son, killed in action in 1941, and endured with composure the illnesses which spoiled his last few years. He will be remembered by many with respect, and by his intimates with the deepest affection. Great sympathy must be felt for his widow, who supported him with love and kindness during the last long illness.

THOMAS GUTHRIE, M.B., B.Chir., F.R.C.S.

Mr. Thomas Guthrie, formerly honorary laryngologist to the Liverpool Royal Infirmary, died at his home in Pembury, Kent, on April 1. He was 82 years of age.

Thomas Guthrie was born in Liverpool on May 3, 1878, and was educated at Sedbergh School and King's College, Cambridge, where he took first-class honours in the National Sciences Tripos. He went on to St. Thomas's Hospital for his clinical training, qualifying in 1903, graduating M.B. in 1904, and taking the F.R.C.S. in 1905. After qualification he held the posts of house-surgeon and clinical assistant in the E.N.T. department at St. Thomas's.

H. V.-F. writes: It was not unusual fifty or sixty years ago for those who had decided to take up the specialty of otolaryngology to gain early experience of it in Vienna, and after ending his studies there Thomas Guthrie returned to Liverpool to join the late Dr. Middlemass Hunt, and eventually to succeed him as honorary laryngologist at the Royal Infirmary. He was also appointed honorary lecturer in laryngology at the University of Liverpool. The opening of the new out-patient building in the Royal Infirmary found the work in otolaryngology rapidly expanding, and in due time an honorary assistant post was created and a certain number of beds were allotted in the hospital. Thomas Guthrie had a busy private practice, a compliment to his clinical judgment and skill as an operator, and his devotion to his hospital work, carried out at times in spite of ill-health, was a fine example of a high sense of duty. I am sure that all his former students who have heard of his death will join me in offering our sympathy to his family.

WILLIAM APPLEYARD, M.B., B.S., F.R.C.S.

Mr. W. Appleyard, former honorary aural surgeon to the Royal Eye and Ear Hospital, Bradford, died on March 31, aged 81.

William Appleyard was born in Bradford on February 7, 1880. Educated at the Bradford Grammar School, he went up to University College Hospital, London, where he distinguished himself by obtaining the gold medal in obstetric medicine and honours in medicine when he graduated M.B. in 1903 and B.S. in 1904. After postgraduate work in Berlin and appointments as house-surgeon at University College Hospital and resident surgical officer at Wolverhampton General Hospital, he obtained the F.R.C.S. in 1907. Appointed clinical assistant at the Royal Eye and Ear Hospital, Bradford, in 1911, he was promoted to assistant surgeon there in 1913, and, after serving as E.N.T. specialist to the B.E.F., he returned in 1918 to become honorary aural surgeon until 1947, when he became honorary consulting surgeon. He was also honorary laryngologist to the Bradford Royal Infirmary and consultant E.N.T. surgeon to the Reedyford Memorial Hospital, Nelson. He retired under the age limit in 1948.

He was a Fellow of the Royal Society of Medicine and a member of the B.M.A. for 50 years, being chairman of the Bradford Division in 1930–1 and vice-president of the Section of Laryngology and Otology when the Annual Meeting of the Association was held in Bradford in 1924. For many years he was also honorary treasurer of the Bradford Medico-Chirurgical Society. His great loves were music and masonry. In the latter he held Grand Lodge rank, while his musical knowledge was profound. A friend of composers and conductors, he was a patron of the Bradford Subscription Concerts for 50 years. He was never happier than when he was following chamber or orchestral music with score in hand.

Shy and reserved, he gave the impression, to those who did not know him well, of coldness. To those privileged to know him intimately he gave a deep and lasting affection as well as loyalty and encouragement. He had suffered grievous tragedy by the death of his son in a motor accident and of his first wife. His second marriage was wonderfully happy, and it was a joy and privilege to belong to their circle of friends. As a patient, a colleague, and a friend I knew him as he really was—warm-hearted, able, sincere, and all that is implied by the term "gentleman." Characteristically he had wished that there should be no mourning for him, yet so many of us had held him in our hearts and could not but absent us from felicity awhile. We will miss him sorely, and to his widow and two daughters goes our deep sympathy.—H. F.

A. J. McD. GRIMSTON, M.B., Ch.B.

Dr. A. J. McD. Grimston, consultant dermatologist to the Royal South Hants Hospital, Southampton, died in Southampton on March 29. He was 60 years of age.

Alfred James McDavid Grimston was born in Manchester on January 21, 1900, the son of a Presbyterian minister. Since 1906 his home had been in Southampton, where he attended King Edward VI School. During the first world war he served with the Royal Naval Air Service, Fleet Air Arm, and on demobilization he began his medical studies at Bristol University, where he graduated M.B., Ch.B. Starting in general practice in Southampton in 1929, he was appointed a district medical officer under the Poor Law in the following year. In 1934 he became a divisional police surgeon and six years later senior police surgeon for Southampton, an appointment that he held until his death. He was also appointed Admiralty surgeon for the port of Southampton in 1934. Becoming clinical assistant to the Dermatological Department of the Royal South Hants Hospital in 1938, he had sole charge of the department on the death of the dermatologist in 1939. But he joined the Royal Navy again for service in the second world war, and when he returned home he retired from general practice to specialize in dermatology, and in 1945 he was appointed consultant dermatologist to the Royal South Hants Hospital, a position he held until his death.

Always active in the interests of his medical colleagues, Dr. Grimston was for many years a member of the Southampton panel committee, which he represented on several occasions at the Annual Conference. A keen member of the B.M.A., he was chairman of the Southampton Division from 1939 to 1942. He was also a past-president of the Southampton Medical Society. His outside interests were catholic—Freemasonry, yachting, shooting, and motor-racing. He was a founder member of the South-western Centre of the Junior Car Club, now known as the British Automobile Racing Club, and it was largely due to his efforts that the centre was re-formed after the war.

His was a genial, kindly personality. His sudden illness last September, culminating in his death, came as a great shock to his many friends and colleagues, for he was much loved, and will be sorely missed in many walks of life in Southampton.

In 1930 he married Dorothy, daughter of the late Henry Wells, J.P., who survives him, and to whom our deep sympathy is extended.—N. W. MacK.

H. C. CORRY MANN, O.B.E., M.D., M.R.C.P.

Dr. H. C. Corry Mann, well known for his nutritional research, and formerly senior physician at the Evelina Hospital for Sick Children, London, died in Guy's Hospital on February 18.

Harold Charles Corry Mann studied medicine at Guy's Hospital and qualified in 1903, graduating M.B. a year later, proceeding M.D. in 1906, and taking the M.R.C.P. in 1907. He held the posts of medical tutor and registrar at Guy's, and was later appointed to the staff of the Evelina Hospital. After the first world war he worked on the staff of the Medical Research Council, studying experimental diets and nutrition in children of school age. He returned later to practice as a consulting physician, but his chief interest was always in nutritional problems.

We are indebted to Dr. H. E. MAGEE for the following appreciation: Corry Mann was a pioneer in nutritional research. It was his feeding test soon after the first world war in an institution for orphan children which demonstrated for the first time the all-round high nutritional value of milk for growing children. Milk had, naturally, been regarded by the medical profession as a good food, especially for children, invalids, and old people; but Corry Mann's investigation made it possible to state in concrete terms the value of milk as a food. The scrupulous care and attention to detail which characterized all his work enabled him to discern that the increased growth rates could not be attributable to the extra calories in the milk supplement, but mainly to the other nutrients, the significance of which subsequent research was to reveal. Corry Mann was truly a pioneer, for he set the pattern for the conduct of investigations designed to test the practical value of foods or of single nutrients, and few of the reports published since his appeared in 1926 have failed to quote the Corry Mann experiment.

After I joined the Ministry of Health in 1933, Corry Mann was clearly among the first on my list to be consulted. He was most helpful, and continued to be so on all the subsequent occasions when I went to him for advice. These meetings, sometimes in the company of others, more often than not took the form of afternoon tea parties, over which he presided with ease, geniality, and courtesy. Conversation would flow freely, and I suppose, because of the man's great good nature, it was not stultified when he would tell one that each scone or cake one selected contained so many calories and so many grammes of protein. He kept account of his diet and would be able to tell one how his weight reacted.

Unfortunately, so far as I know, none of his records was ever published, but those of us who were concerned just before and in the early days of the last war with the planning of war-time food policy found his records helpful. He was a gentle little man, quite unassuming, and with little or no desire for publicity, but always approachable and friendly.

S. D. KILNER, M.D., D.M.R.E.

Dr. S. D. Kilner, who practised first in Llandudno, and then for thirty years in Bury St. Edmunds, died in the West Suffolk General Hospital on April 6, aged 72.

Strangman Davis Kilner was born on December 1, 1888, the fourth son of Dr. Charles S. Kilner, M.B.E., also of Bury St. Edmunds. He was educated at Derby Grammar School, and Emmanuel College, Cambridge, where he took both parts of the Natural Sciences Tripos, gaining first-class honours in the first part. For his clinical training he went to the Middlesex Hospital, where he qualified in 1914. Shortly afterwards he joined the R.N.V.R. and served in the Royal Navy through the first world war. After demobilization he returned to the Middlesex Hospital, becoming medical registrar there after holding house appointments. He graduated M.B., B.Chir. in 1918 and proceeded M.D. in 1922.

He entered general practice in Llandudno in 1922 and worked there until 1928, when, on the death of his brother, the late Dr. H. Goff Kilner, he came to Bury St. Edmunds to become the fourth successive Kilner to work in a practice which has been extant for over one hundred years. He also held appointments as physician and radiologist at the West Suffolk General Hospital, obtaining the D.M.R.E. in 1935. On the formation of the Emergency Medical Service he was appointed consultant physician and radiologist, which posts he held until the introduction of the N.H.S., when he became consultant radiologist to the West Suffolk hospital group. Relinquishing this appointment in 1956 on reaching the age limit, he worked for a further two years in general practice and retired in 1958.

"Taddy" Kilner was a man of high intellectual ability who, but for the process of events, might have attained consultant rank at a high level. He was a man of foresight and tenacity of purpose, using these qualities to advantage for the hospital and in developing his practice. In his hospital practice he built up the *x*-ray work from small beginnings to a department fully equipped to meet the needs of a provincial general hospital and to provide a full service always available to the neighbouring general practitioners. As a physician, his medical work was a great joy to him and many benefited by his diagnostic acumen and skill, and it was with great reluctance that he relinquished his medical work on the introduction of the N.H.S. In his thirty-seven years of general practice there was full scope for his fine personality. He was counsellor and friend as well as medical adviser to his patients. Intolerant of injustice, he fought many a battle for the underprivileged. His thoughtful kindliness, combined with his deep religious conviction, made him a source of comfort and strength to many.

He leaves a widow and three daughters, to whom goes the sympathy of his many friends.—H. A. W. and E. J. C.

A. M. M. GRIERSON, O.B.E., M.D., D.P.H.

Dr. A. M. M. Grierson, deputy Medical Officer of Health of the City of Manchester and Manchester Port Health Authority, died in hospital after a very short illness on April 13 at the age of 59.

Alexander Millar Meek Grierson was born on November 6, 1901, the younger son of the late Sir Andrew Grierson, town clerk of Edinburgh. Educated at George Watson's College and the University of Edinburgh, he graduated M.B., Ch.B. in 1923, obtained the Diploma in Public Health in 1924 and proceeded to M.D. with high commendation in 1928. He was a Fellow of the Royal Society of Edinburgh. Like so many of his contemporaries in Scotland at the time of graduation, Grierson unhesitatingly chose public health as a career from the beginning. He joined the staff of the bacteriological department at Edinburgh University and a little later was appointed assistant medical officer of health in the public health department of the City of Edinburgh and the Port of Leith.

In 1935, when the City of Manchester began an intensive drive on bad housing, a new appointment of Senior Medical Officer for housing was made. Grierson was appointed and worked hard and happily in the health department—a valued colleague of the late Dr. Veitch Clark, the medical officer of health, he too being a graduate of Edinburgh University. The outbreak of war caused the suspension of the housing programme, and Grierson was thus immediately available to deal with the medical direction of air-raid precautions at first and later with the medical arrangements necessitated by the heavy air raids on Manchester, in 1940 in particular. He served faithfully and diligently on this work during the whole of the war and for his services was appointed O.B.E. After the war, he was senior medical officer in general administration in the Manchester public health department and succeeded the late Dr. W. St. C. McClure as deputy medical officer of health in 1947. He was president of the North-West Branch of the Society of Medical Officers of Health in 1951. Dr. Grierson leaves a widow, to whom we extend our sympathy.

Dr. C. METCALFE BROWN, medical officer of the City of Manchester, writes: Grierson was a splendid colleague. He had a flair for administration and was responsible for much of the routine central administration, including the preparation of the annual report on the health of the city. He was a genial man—courteous, sympathetic, and helpful. The problems of the aged and infirm were one of his first cares, and his reputation for his wise and gentle handling of these cases was widely recognized. His integrity was complete and invincible, and for his great and unstinted loyalty I personally have had much reason to be grateful. The officers of the department, senior and junior alike, found him approachable and kind. His greatest interest away from the office was his home and garden—he and his wife were keen and expert gardeners, and he enjoyed nothing better than discussing at length with many of his friends the results, the delights, and vagaries of his garden flowers. His illness and unexpected death has shocked the department and all his associates in the Town Hall—for me this sudden break in a pleasant daily association for 19 years is a heavy loss indeed.

Dr. Grierson is survived by his wife.

W. S. SYKES, M.B.E., M.B., B.Chir., D.P.H., D.A.

Dr. W. S. Sykes, who was formerly in general practice in Morley, near Leeds, and anaesthetist to the General Infirmary and other hospitals in Leeds, died suddenly on March 31. He was 66 years of age.

William Stanley Sykes was born on August 5, 1894, and was educated at Rossall School, Emmanuel College, Cambridge, and St. Bartholomew's Hospital. Before qualifying in 1919 he served as a surgeon probationer in the R.N.V.R. After holding resident appointments at Bart's, including that of house anaesthetist, he graduated M.B., B.Chir. in 1921, took the D.P.H. in the same year, and then settled down in general practice in his home town of Morley. His interest in anaesthetics led to his appointment as honorary anaesthetist at the Leeds General Infirmary and at several other local hospitals. He obtained the Diploma in Anaesthetics in 1935. At the outbreak of the second world war he immediately volunteered for service in the Army as an anaesthetist and was granted the rank of major. He was taken prisoner of war in the campaign in Greece and as such continued to serve the Allied troops as anaesthetist in

the hospital of Stalag 8B, for which he was later appointed M.B.E.

He was well known as an author. His first book on general practice was followed by a series of detective novels with a medical background. The best known of these was *The Missing Moneylender*, which found a large market here and in the United States. Since the end of the war he devoted much time to research into the history of anaesthetics, and this resulted in the publication in 1960 of the first volume of *Essays on the First Hundred Years of Anaesthesia*. He retired from general practice in 1959 but continued to serve as chairman of the Ministry of Pensions Board at Leeds.

Stanley Sykes was a man of quiet and retiring disposition, but those who knew him well were impressed by his wide general knowledge, his varied interests, his hospitality, and his kindness. During the last year he suffered ill-health, but remained cheerful and active, being helped in this by his devoted wife.

S. G. DE C.-L. writes: In 1927 Dr. Sykes published his first book, *A Manual of General Medical Practice*, a vademecum for the young general practitioner, but his great love was anaesthesia. He had at this time already contributed an article on ethyl chloride to the thirteenth edition of the *Encyclopaedia Britannica*. In 1931 he published his first book on anaesthetics in the Modern Treatment Series. Not only was Sykes a great enthusiast and prolific writer on the subject of anaesthesia, but his very logical mind led him in this period to writing thrillers as a relaxation. His first book, *The Missing Moneylender*, was eventually published in the Penguin series. Two other thrillers he wrote were entitled *The Ray of Doom* and *The Harness of Death*.

Sykes was a perfectionist, and, when it was possible, would accept nothing but the best. As a result of this, on his return to Leeds after the second world war he was so dissatisfied with the department of anaesthesia that he issued an ultimatum that unless conditions were considerably improved he would resign—and resign he did. Being who he was, Sykes from that moment gave up anaesthetic practice completely and returned to general practice, and devoted the rest of his life to the production of his *chef d'œuvre—Essays on the First Hundred Years of Anaesthesia*, the first volume of which was published last year, the second being at the moment in the press. The remaining volumes will be published posthumously.

His many friends throughout the world will regret the passing of a brilliant and logical brain and a great friend.

M. C. L. SMITH, *M.C.*, M.B., B.S.

Dr. M. C. L. Smith died suddenly at Midhurst on March 21 after a long illness bravely borne. He was 53 years of age.

Michael Carson Lyndon Smith upheld the prestige of his family medical tradition. His grandfather, Sir Thomas Smith, Bt., K.C.V.O., surgeon to St. Bartholomew's Hospital and vice-president of the Royal College of Surgeons, was Serjeant Surgeon to both Queen Victoria and King Edward VII. His father, Dr. Gilbert Smith, practised for many years at Hindhead, and was, with Mrs. Gilbert Smith, much beloved by a wide circle of patients and friends. As his father and grandfather had done before him, Michael Smith became a medical student at St. Bartholomew's Hospital, and in 1934 qualified M.R.C.S., L.R.C.P. and also graduated M.B., B.S.(London) in the same year. Having completed residential medical hospital appointments, he was commissioned in the Indian Medical Service in 1936. His interest in all types of people and his strong character and friendly humour fitted him for the responsibilities he then had to undertake. In his early days of service in India there was opportunity for recreation, and on one occasion against everyone's advice he entered and rode to win (at 30 to 1 against) a horse which had only one seeing eye.

During the second world war and after, Lieutenant-Colonel Smith, as he became, saw active service in many theatres of war. In Eritrea an advanced post of British troops had become cut off and under heavy fire: Michael Smith reached this unit with medical aid and tended the wounded until a relieving force arrived. He was recommended for the highest possible military decoration, and an immediate award of the Military Cross was then made to him at Keren. He was also mentioned in dispatches, and served in the Middle East, in the Western Desert, and in Burma. Lieutenant-Colonel Smith was with the first occupation forces in Japan after Hiroshima.

When the partition of India came Michael Smith left the Indian Medical Service, but his desire was always to work abroad, and in 1947 he returned to India to give voluntary help in dealing with the refugee problem. Later, in 1951, he went for some years to Korea, working first with the Red Cross and later with the United Nations Korean Rehabilitation Agency. During this time he became impressed by the widespread devastation caused by leprosy, and concentrated on the control and treatment of this disease in Korea and also in Hong Kong.

It was as a worker among lepers that he went to Thailand under the auspices of World Health Organization in 1958, and there remained for two years. In the East the need for skilled medical men to save large populations of under-nourished people prone to disease was a fact from which Michael Smith would probably never have turned away. In his final illness he maintained his lively interest in world affairs and in those around him, and to the end his morale was of the highest order.

In 1936 he married Pauline, daughter of the late Charles H. Rowlatt, of Headley. There were five children of the marriage—one son, now a medical student at Cambridge, and four daughters. To his widow and family, who live at Headley Grange, Headley, Bordon, Hants, we offer our profound sympathy.

R. H. ENOCH, M.R.C.S., L.R.C.P.

Dr. R. H. Enoch, who had practised in Guildford for the past thirty years, died suddenly on April 1 after a short illness. He was 64 years of age.

Robert Henry Enoch was born at Tonyrefail, Glamorganshire, on January 8, 1897, the son of Daniel Enoch, J.P. After leaving Cardiff High School he began his medical studies at the University College of South Wales, Cardiff, and went on to St. Bartholomew's Hospital for his clinical training. After qualifying in 1923 he spent the next eight years in resident hospital posts at the Cardiff Royal Infirmary, mainly in the surgical and otolaryngological departments. His final appointments there were as registrar and deputy medical superintendent. When the B.M.A. held its Annual Meeting in Cardiff in 1928 he was honorary secretary of the Section of Dermatology.

In 1931 he settled in general practice at Guildford, where he soon became very popular with both colleagues and patients. His work was interrupted in 1939 by the war, during the whole of which he served in the Royal Navy, retiring as surgeon commander, R.N.V.R. Returning to practice, he soon re-established himself in the affections of all the people around him. He took an active part in all medical activities, including the B.M.A. He was chairman-elect of the Guildford Division and served for many years both as a member and vice-president of the Surrey Branch Council. He was formerly honorary anaesthetist at the Royal Surrey County Hospital and a member of the medical advisory committee.

An able and widely experienced practitioner and a genial and kindly companion, Dr. Enoch will be sadly missed by colleagues and patients alike. He leaves a widow and three stepchildren, who are all engaged in the practice of medicine. —J. O. M. R.

A. M. McMULLAN, M.D., B.Sc., D.P.H.

Dr. A. M. McMullan, who was in general practice in Leicester for 38 years, died in the London Hospital on September 15, 1960, after a brief illness. He was 65 years of age.

Alexander McDonald McMullan was born in Belfast on November 10, 1895, and received his early education at Campbell College. Later he became a medical student at Queen's University, Belfast, and graduated M.B., B.Ch. in 1917. After an appointment as house-surgeon at the Royal Victoria Hospital, Belfast, he attended a course on war neuroses at the Military Hospital, Maghull. This led to his appointment as medical superintendent at the Leicester Neurasthenic Hospital (Ministry of Pensions) in 1918. He proceeded M.D. in 1920, and in the same year took the degree of B.Sc. with first-class honours. In 1922, the hospital having completed its work for shell-shocked soldiers, he decided that his future lay in general practice, and by a stroke of good fortune he was able to buy a practice in Leicester. As a striking memorial and tribute to his life's work as a general practitioner of the best type, it need only be recalled that the practice now requires no fewer than seven partners. Nevertheless, he worked for and obtained the D.P.H. (Cambridge) in 1929. He was proud to boast that he qualified for the reduced annual subscription to the B.M.A. as a member of not less than 40 years' standing. Indeed, at the time of his death, he was the president of the Leicestershire and Rutland Branch, an office which gave him the greatest pleasure and satisfaction. He was also a distinguished past president of the Leicester Medical Society.

It is no exaggeration to say that Dr. McMullan possessed all the qualities of heart and mind that go to make a first-class family doctor. He was an excellent clinician, with a wide knowledge of therapeutics, and a wise and sympathetic counsellor, the possessor of a wonderful memory and a very charming personality. It is easy to understand why he gained the confidence and affection of his patients, and the esteem and respect of his colleagues, whether general practitioner or consultant.

He was a founder member and past president of the Leicester Ulster Society. As a Freemason he was a very senior and active member of a number of Degrees in the Province of Leicestershire and Rutland, where his deep, rich, and impressive voice will be sadly missed. He was a keen and enthusiastic golfer and was a past captain of one of his two local clubs. Indeed, he played his last round the day before he left for the London Hospital. As a bridge player, too, he had a high reputation. He was a very congenial companion, an excellent raconteur, and a great lover of his fellow men. He had a very full life, and in return he contributed in good measure to the life of the city of his adoption. He was so widely known and such was his popularity that at his memorial service the Cathedral was filled with representatives of all walks of life from the city and county. The Very Reverend Mervyn Armstrong, formerly provost of the Cathedral and now the Bishop of Jarrow, came down specially to deliver a deeply moving tribute to Dr. McMullan's memory.

To his widow, daughter, and son, who is now assistant senior medical officer of the South-east Metropolitan Regional Hospital Board, we offer our deep sympathy in their grievous loss.—E. W. G.

GEORGE SMITH, M.B., C.M.

Dr. George Smith, who celebrated his 100th birthday last month, died on April 14. He had been living recently at St. Agnes in Cornwall, but before that he had practised for many years in Henley-on-Thames.

George Smith was born at Keir, Dumfriesshire, on March 9, 1861, and was educated at Framlingham College and at the Universities of Edinburgh and Vienna. He graduated M.B., C.M. with honours at Edinburgh in 1885. Thereafter he practised for a few years at Acton and then moved to Henley-on-Thames, where he remained from 1888 to 1944. He retired because of ill-health in 1945 and went to live in Cornwall about three years ago, to be near his son. Dr. Smith's wife died in 1952. His sister also attained a great age, dying 18 months ago on her 105th birthday.

V. B. GREEN-ARMYTAGE, M.D., F.R.C.P., F.R.C.S. F.R.C.O.G.

The obituary of Mr. Green-Armytage was published in the *Journal* of April 22 (p. 1176).

C. H. B. writes: The sudden passing of "G.A.," as he was affectionately known to hosts of his friends and admirers, has come as a profound shock to me and very many others. A close and valued friend and colleague for over forty years, his loss to me is irreparable, and it will be keenly felt by his numerous patients, the vast majority of whom adored him. His gay spirit, his wit, and his generosity will be sadly missed both in private and in public.

As an after-dinner speaker he was much in demand, and his amusing stories were eagerly looked forward to and enjoyed. His absence at the next I.M.S. dinner will cast a gloom over the occasion. He worked at high pressure until shortly before his death, lecturing and operating all over the world. His abounding energy amazed us all. Others will tell of his achievements, his three Fellowships and academic honours, that were awarded him. Why his work of such outstanding merit and value to nation was never officially recognized remains a mystery to us all.

The old I.M.S. has lost one more of its outstanding members and the gynaecological world one of its most notable exponents.

Medico-Legal

OPHTHALMIC INJURY

[FROM OUR LEGAL CORRESPONDENT]

On March 20, at the Glamorganshire Assizes, Mr. Justice McNair gave judgment for the defendants in a negligence action brought by a workman who had lost his eye against persons responsible for his treatment (*Jones* v. *The Welsh Regional Hospital Board and Kemp*). Counsel for the defendants were instructed by Messrs. Hempsons, solicitors for the Medical Defence Union.

Penetration by Foreign Body

On an afternoon in June, 1956, the plaintiff, while using a hammer and punch, felt something strike his right eye. Finding his vision impaired, he went straight to the West Wales General Hospital at Carmarthen: there he was seen by the duty casualty officer, who had in fact no postgraduate training in ophthalmology. The casualty officer found a small corneal laceration and defective vision, and reported her findings immediately to Mr. G. S. Forrester, a consultant ophthalmologist attached to the Llanelly Hospital (Carmarthen Hospital had no eye unit of its own). It was arranged that the plaintiff should be sent to Mr. Forrester's consulting-rooms in Llanelly the next morning. When the plaintiff consulted Mr. Forrester the next morning it was found that there had been penetration by a minute piece of metal into the vitreous chamber of the eye. Mr. Forrester also found gross infection of the anterior and posterior chambers of the eye. He immediately removed the foreign body, admitted the patient to Llanelly Hospital, and prescribed atropine sulphate drops, "terra-cortril" drops, and systemic penicillin. During the first five days in hospital, owing to some unexplained error, no systemic penicillin was given. The infection in the eye did not respond to treatment, and the eye was removed a little less than a month after the accident.

Negligence Alleged

The casualty officer was alleged to have been negligent in two respects. Firstly, it was alleged that she did not communicate promptly with the consultant ophthalmic surgeon, and, secondly, it was alleged that she was negligent in not taking a full and accurate history from the plaintiff. Both of these allegations were disproved as matters of fact.

No charge of negligence was made against Mr. Forrester, but the regional hospital board was charged with negligence in having failed to administer the prescribed systemic penicillin. Since the board admitted the early failure to administer penicillin, the only question for the court was whether any damage to the plaintiff followed from that failure. The court found as a fact that by the evening of the day of the accident the whole of the eye was in an advanced state of virulent infection. The failure to administer penicillin thus, at the worst, could have deprived the plaintiff only of the hope of saving his eye.

Expert Evidence

Was there any real chance of the eye being saved after the day of the accident? If so, could it have been saved by penicillin? Evidence was given by Mr. Forrester, Mr. M. H. Whiting, and Mr. O. Gayer Morgan that they had no experience of a case where an eye infected to a similar degree had ever been saved. Mr. A. G. Palin, giving evidence for the plaintiff, admitted that an infected vitreous was a very bad sign, but denied that it involved the doom of the eye, and referred to two cases treated in the Bristol hospitals where bad cases of panophthalmitis had been cured by the administration of antibiotics. However, it could not be shown that it was penicillin, as opposed to other antibiotics, which worked the cure. Mr. Forrester said that he prescribed penicillin, not to cure the virulent infection in the eye, but because he hoped to confine the infection to the eye and to stop it spreading into the general blood-stream. On that evidence, Mr. Justice McNair found that by the evening of the day of the accident there was no prospect of the eye being saved.

"Loss of a Hope"

On this finding of fact, Mr. Justice McNair was relieved of the task of deciding the question of law whether the loss of a hope is sufficient damage to the plaintiff to found an action in the fact of negligence. The learned judge did state, however, that while he preferred to express no concluded opinion, he was of the view that the loss of a hope can properly be regarded as sufficient damage to found an action, "but before effect could be given to it, the hope must be a measurable hope, and if the hope is so remote that it can only be expressed by phrases such as 'one in fifty or more' and 'one in a hundred,' I should doubt, as at present advised, whether that is sufficient proof of the existence of the hope to justify a finding against a defendant."

Medical Notes in Parliament

"MEALS ON WHEELS"

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Armed with the experience of the W.V.S., of which she has been a distinguished leader, and attracting to her standard everyone who spoke, Lady SWANBOROUGH besought the Government on April 18 to extend the "Meals on Wheels" service as a contribution to the care of the homebound and to authorize local authorities to provide kitchens, other equipment, and facilities for voluntary bodies operating "meals-on-wheels" schemes. In one sentence, her case was this: it would be of infinite value to the voluntary organizations if local authorities were to have some arrangement by which these schemes could be simultaneously assisted, under both the National Assistance Act, 1948, and the National Health Service Act, 1946, so that each and every scheme could be used to best advantage in meeting the needs of the sick and the handicapped as well as those of the aged.

Statutory Powers

Section 31 of the Assistance Act permitted a local authority to contribute to the funds of any voluntary organization whose activities consisted in or included the provision of recreation or meals for old people. Most "meals-on-wheels" schemes, she said, were operated under this Act for the benefit of people of pensionable age who were unable to provide adequate meals for themselves. So far as the voluntary organizations could discover from their negotiations with local authorities, there was no clear ruling whether Section 31 enabled local authorities to incur capital expenditure to provide kitchens, vans, etc.; and in any event the Act restricted the provision to old people. The powers given by section 28(3) of the Health Service Act were restricted to local health authorities—counties or county boroughs—and permitted meals to be supplied to people of any age if they were sick, or likely to become sick, for want of proper provision. Expenditure under the 1948 Act came from the rates; that under the 1946 Act ranked for the general Exchequer grant. What was urgently needed was to get the legislative gap closed.

Medical Views

Lord AMULREE, formerly chairman of the "Invalid Meals for London," and co-author of an article on the subject in the *British Medical Journal*,* advocated a comprehensive meals service, available five days a week and comprising both special and normal meals. It should have a medical background, and should be provided under the Health Service Act. Lord TAYLOR said the issue was whether this work should be done by voluntary organizations or the local authorities. It was a difficult problem to resolve, because both did excellent work. But where a job was being done well, to take it away from a voluntary organization for reasons of statutory tidiness was a great mistake. He doubted whether fresh legislation was needed, provided that the existing Act was interpreted liberally. Lady SUMMERSKILL expressed amazement at learning that there had been administrative difficulties over the modest request for a subsidy which could do something to reduce the pressure on the costly hospital service.

For the Government Lord ST. OSWALD said the Minister of Health had already given—on November 10, 1959—an assurance that the Government proposed introducing legislation on behalf of the elderly, which would enable local authorities to use their privately run accommodation and to make direct provision of meals. Since then there had been the report of the Government Social Survey. The Minister was now considering, in the light of discussion and the report, what would be the best way to give effect to the undertaking. There was some confusion about the powers local authorities had under existing legislation to assist voluntary bodies. The phrase "Suffering from illness or its after-effects" in the National Health Act was the limiting factor which prevented all cases being dealt with. If any local authority requested the Ministry's views of the authority's powers under an Act of Parliament they were always willingly given. What they would all like to see was some advance on what was possible under existing law.

QUESTIONS IN THE COMMONS

Beds Closed for Lack of Staff

The MINISTER OF HEALTH was asked by Mr. C. A. HOWELL (Birmingham, Perry Bar, Lab.) on April 17 how many hospitals and wards were out of use because of lack of nursing staffs in each region. Mr. ENOCH POWELL told him that figures were available only in terms of beds unused for lack of staff of all kinds. The total figures at the end of

*Amulree, Lord, and Palfrey, Alison, *Brit. med. J.*, 1958, 1, 1498.

1959 (which were the latest available) were 10,417, including 53 in teaching hospitals. The regional figures were: Newcastle, 224; Leeds, 613; Sheffield, 727; East Anglian, 214; North-west Metropolitan, 890; North-east Metropolitan, 1,019; South-east Metropolitan, 2,155; South-west Metropolitan, 868; Oxford, 379; South Western, 256; Wales, 453; Birmingham, 1,137; Manchester, 1,150; Liverpool, 76; and Wessex, 203.

Mr. Powell also stated that a total of some 21,000 vacancies for hospital nurses of all grades was current at offices of the Ministry of Labour at December 31, 1960. A breakdown of this figure by regional hospital areas was not available. The number of staff in post at September 30, 1960, was the highest ever recorded, and he saw no reason for a special inquiry into recruitment and wastage.

Barbiturates and Alcohol

Lieutenant-Colonel J. K. CORDEAUX (Nottingham, Central, Con.) asked the Minister on April 17 how many deaths had been caused, or possibly caused, during the past two years, from any convenient date, by the combination of barbiturate drugs and alcohol, both consumed within a short period of time. Miss EDITH PITT, Parliamentary Secretary, replied that 232 deaths in 1959 were assigned to accidental poisoning by barbiturates, and 19 of these were stated to be associated with consumption of alcohol. Provisional figures for 1960 were 293 and 48 respectively. The returns did not indicate within what period the drugs and alcohol were consumed.

Drugs and Driving

Sir WALTER BROMLEY-DAVENPORT (Knutsford, Con.) asked, in view of the prospective changes in the law with regard to driving under the influence of drugs and alcohol, what information had been made publicly available by the Ministry about what drugs and in what quantities could impair the human ability to drive motor vehicles; what drugs could be obtained without prescription which in certain quantities and conditions could be dangerous in this connexion; and what steps were taken in connexion with Health Service prescriptions to warn patients about this aspect of the drugs prescribed for them. Mr. POWELL said in answer, "None." Most such drugs were restricted to supply on a doctor's prescription, and it was his responsibility to warn his patient of the risks of driving after taking them. Doctors were reminded of this in their comprehensive prescribing handbook.

Intoxication Record in Road Accidents

Mr. J. DEMPSEY (Coatbridge and Airdrie, Lab.) asked the Minister of Transport on April 19 for figures showing how many fatal road accidents occurred in each of the last 10 years as a result of which drivers were convicted who were under the influence of drink at the time of the accident. Mr. E. MARPLES supplied the following statistics, explaining that they showed, for Great Britain as a whole, up to 1958 the total number of accidents in which intoxicated drivers and riders were reported by the police to be a contributory factor. For 1959 and 1960, as a result of a change in the accident reporting system, the figures related only to the number of fatal and serious-injury accidents as a result of which a driver or rider was charged with a drink offence under the Road Traffic Acts, or would have been so charged but for the death or serious injury of the person concerned. It was not possible to provide comparable figures showing the number of convictions obtained.

Year	Fatal, Serious, and Slight Accidents	Fatal and Serious Accidents
1951	1,013	
1952	870	
1953	795	
1954	826	
1955	934	
1956	994	
1957	1,096	
1958	1,102	
1959		423
1960		432

Diphtheria Cases and Deaths

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked the Minister of Health on April 17 what were the numbers of diphtheria cases and deaths recorded in immunized and unimmunized persons, respectively, in the different age groups in the years 1955–60, and what was the percentage in each age group which had been immunized at the time. Miss PITT stated that this information was not available by age groups. The totals were as follows:

Year	Diphtheria Cases		Diphtheria Deaths	
	Fully Immunized	Unimmunized or Not Fully Immunized	Fully Immunized	Unimmunized or Not Fully Immunized
1955	34	121	0	13
1956	11	42	1	7
1957	6	31	0	4
1958	25	55	1	7
1959	38	64	0	0
1960	4	45	1	4

Note. A person was regarded as fully immunized if he had concluded a primary course or received a reinforcing inoculation within the previous five years.

Oral Polio Vaccine

Mr. DINGLE FOOT (Ipswich, Lab.) asked the Minister of Health on April 19 for a statement regarding the future availability of stocks of oral vaccine for emergency use in communities or areas where poliomyelitis became, or showed signs of becoming, prevalent. Mr. POWELL answered that an adequate quantity was available for immediate use if this situation arose.

Universities and Colleges

UNIVERSITY OF BIRMINGHAM

The title of University Senior Clinical Tutor in Paediatrics and Child Health has been conferred on Dr. J. S. Oldham.

Dr. J. H. Edwards has been appointed Clinical Lecturer in the Department of Social Medicine from October 1, 1961, and Dr. P. Johnson Research Fellow in the Department of Medical Biochemistry and Pharmacology from April 1, 1961.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the Faculty held on April 10, with the President, Dr. J. H. Wright, in the chair, the following were admitted Fellows of the Faculty: *qua* Physician, M. A. Almani, M. Aslam, M. A. Q. Faiz, J. M. Macfie, P. McKenzie, M. K. Pai, S. D. S. Park, R. Ramkisson, R. H. Shah, J. A. Thompson, C. G. Uragoda, Q. A. M. M. Zaman; *qua* Surgeon, W. C. Brown, B. R. Das, A. A. Efunkoya, F. H. Ghali, M. A. Siddiqui, A. C. Smith.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the College by the Council on February 18:

J. Bell, I. Cher, T. J. Connelley, B. D. Cooke, J. Y. Crooks, J. D. Crowley, J. R. Dalton, R. E. Dunstan, W. J. Garrett, D. S. Gibson, P. Gibson, R. S. Gye, H. M. Hadley, F. J. Ham, D. Howell, J. L. C. Lahz, G. A. D. Lamb, J. A. McArthur, G. M. McFadden, E. D. McIntyre, E. V. Mackay, R. O. Mackay, M. B. Menelaus, J. D. H. Muir, L. S. Parker, D. Pfanner, G. J. Pollock, G. R. A. Raad, D. Rabinov, J. F. Sander, G. J. Schnitzler, J. R. Solomon, J. Sunderman, J. R. Thomson, J. G. Teakley, J. P. Tonkin, Y. L. Tseng, J. Upsdell, J. B. Walker, F. R. Wilson, R. P. Yaxley, J. D. N. Yelland.

FACULTY OF ANAESTHETISTS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the Faculty of Anaesthetists, Royal Australasian College of Surgeons, by the Council on February 18:

G. J. Carroll, H. W. K. Chan, R. H. S. Connock, Barbara P. Coppen, H. R. P. Coutanceau, J. Davenport, F. Fisher, J. F. A. Forster, R. M. Hart, N. Potter, B. E. Sharkey, J. G. Stocks, I. A. Waldie.

Vital Statistics

Lobar Pneumonia in Decline

Lobar pneumonia is a disease which has responded well to treatment by sulphonamides and antibiotics. The World Health Organization has prepared this table to show the percentage decrease in deaths from lobar pneumonia in the years 1953–7 compared to the number of deaths recorded in the years 1931–5:

	Men %	*Women* %
Canada	75.1	80.2
U.S.A.	81.8	83.8
Japan	73.4	71.4
Denmark	84.2	82.2
Italy	95.8	95.5
Norway	87.2	85.3
Netherlands	72.7	67.2
England and Wales ..	71.7	65.8
Scotland	79.1	70.5
Switzerland	89.9	90.4
Australia	59.1	63.5
New Zealand ..	72.5	67.5

Population of Ceylon

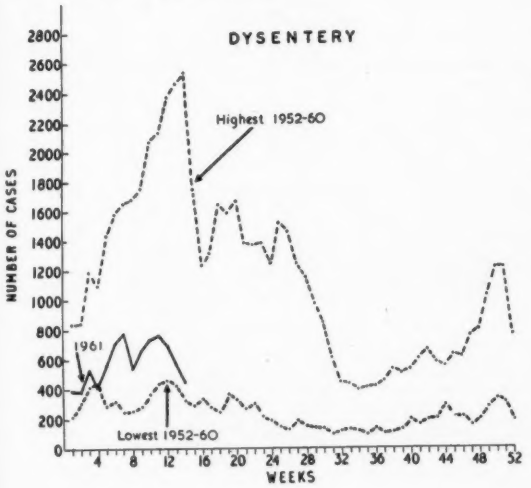
The estimated population of Ceylon at the middle of 1959 was 9,612,000; this was an increase of over 2m. since 1950. The birth rate in 1959 was 36.9 per 1,000 population, and the death rate 9.1. The infant and maternal mortality rates for 1959 are not yet available, but in 1958 the infant mortality rate was 64 per 1,000 live births, the lowest figure yet recorded. The maternal mortality rate was 3.9 per 1,000 live births.—*Administration Report of the Director of Health Services for 1959*, Colombo, Ceylon.

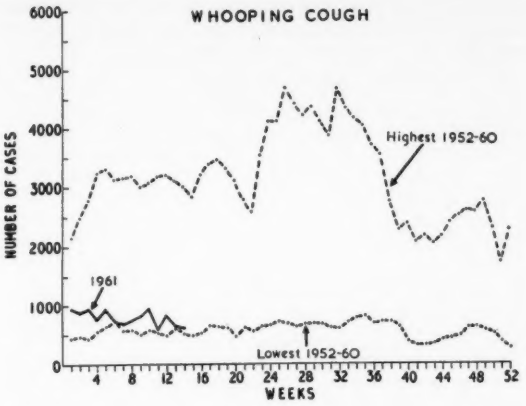
Population of Australia

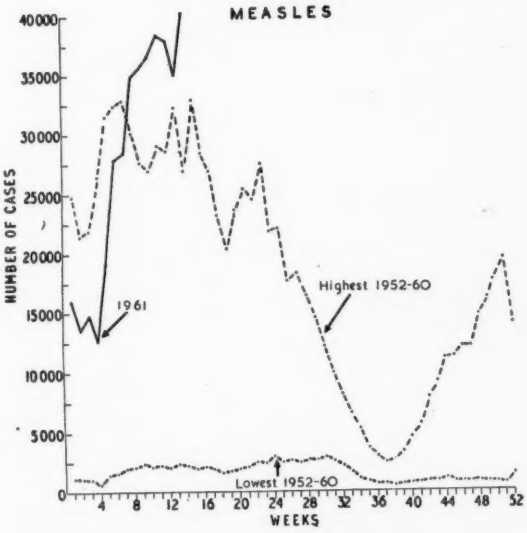
The population of Australia gained 230,000 in 1960 and is now approaching 10,500,000. New South Wales is the most populous state with 3,870,000 people, followed by Victoria with just over 3,000,000.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases During the First Quarter

The notifications of measles during the first quarter of 1961 reached a record high level (353,695), the previous highest figure being 350,836 in 1953. A further fall was recorded in the notifications of acute poliomyelitis, which were the lowest since the disease assumed epidemic proportions in 1947. The number of notifications of dysentery was only half of the number in recent first quarters, but the incidence is still very high. The incidence of scarlet fever also was low compared with previous years. Diphtheria showed a disturbing rise, although the actual number of cases is still small. A comparison of the uncorrected notifications for the first quarters of the last five years is:

	1957	1958	1959	1960	1961
Measles	233,826	49,359	271,651	23,466	353,695
Scarlet fever ..	10,315	10,735	15,198	14,512	6,483
Whooping-cough ..	38,251	7,442	7,989	11,236	10,789
Acute poliomyelitis	516	292	217	84	56
Diphtheria	59	39	44	45	73
Meningococcal infections	385	389	384	278	319
Dysentery	13,594	13,861	13,618	19,857	7,730
Acute pneumonia ..	8,491	11,351	17,744	5,900	11,408
Enteric (paratyphoid and typhoid fevers	94	75	193	57	49
Deaths from influenza	361	2,093	7,098	504	6,377

Road Casualties in February

In February, 1961, the number of people who died as a result of road accidents was 415. Of this total, 175 were pedestrians, 43 pedal-cyclists, 84 motor-cyclists, scooterists,

or moped riders, and 113 drivers or passengers in cars and other vehicles. Compared with last year child pedestrian casualties showed an increase of 10%.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

Measles	Week Ending April 8	Week Ending April 15
Durham	1,776	**1,491**
Gateshead C.B.	256	**230**
Essex	2,978	**2,999**
West Ham C.B.	308	**364**
Hornchurch U.D.	285	**328**
Gloucestershire	814	**899**
Bristol C.B.	456	**558**
Hampshire	1,883	**2,589**
Portsmouth C.B.	406	**517**
Southampton C.B.	224	**260**
Havant and Waterloo U.D.	212	**883**
Kent	2,154	**1,708**
Lancashire	2,230	**2,069**
Liverpool C.B.	145	**200**
Manchester C.B.	288	**245**
Lincolnshire	799	**943**
Grimsby C.B.	315	**409**
London	2,857	**2,391**
Lewisham	283	**199**
Wandsworth	214	**306**
Woolwich	270	**178**
Middlesex	2,641	**2,629**
Ealing M.B.	354	**255**
Northamptonshire	657	**753**
Northampton C.B.	475	**514**
Northumberland	708	**792**
Newcastle upon Tyne C.B.	242	**385**
Staffordshire	1,913	**2,368**
Stoke-on-Trent C.B.	183	**207**
Walsall C.B.	312	**257**
Newcastle-under-Lyme M.B.	151	**221**
Surrey	1,692	**1,675**
Croydon C.B.	370	**237**
Warwickshire	2,627	**2,678**
Birmingham C.B.	1,190	**1,309**
Coventry C.B.	353	**437**
Yorkshire East Riding	712	**524**
Kingston upon Hull C.B.	449	**301**
Yorkshire West Riding	2,603	**2,830**
Huddersfield C.B.	217	**250**
Leeds C.B.	232	**372**
Sheffield C.B.	451	**416**
Glamorganshire	1,244	**900**
Cardiff C.B.	538	**391**
Dysentery		
Lancashire	67	**88**
Irlam U.D.	0	**28**
Nottinghamshire	14	**27**
Beeston and Stapleford U.D.	10	**18**
Yorkshire East Riding	19	**30**
Beverley M.B.	11	**16**
Yorkshire West Riding	89	**88**
Leeds C.B.	16	**21**
Acute poliomyelitis		
Suffolk	2	**5**
Ipswich C.B.	2	**4**
Paratyphoid fever		
Edinburgh	1	**5**
Diphtheria		
London	2	**3**
Battersea	1	**3**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 8** (No. 14) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire
Diphtheria	5	2	1	0		3	0	0	1	
Dysentery	449	43	164	7	15	2,535	271	215	24	10
Encephalitis, acute	2	1			*	3	1	0	0	
Enteric fever:										
Typhoid	3	1	0	0		0	0	0	0	
Paratyphoid	1	0	1(B)	0		3	0	0	1	
Food-poisoning	104	21	12	1		229	45	10		
Infective enteritis or diarrhoea under 2 years				19	28				12	35
Measles*	40,435	2857	561	512	311	2,143	70	70	5	21
Meningococcal infection	19	4	9	1	1	24	1	7	1	1
Ophthalmia neonatorum	16	0	4	0		25	4	4	0	
Pneumonia†	312	23	161	4	1	465	21	190	3	5
Poliomyelitis, acute:										
Paralytic	8	1	0	0		2	0	0	0	1
Non-paralytic	0	0	0			0	0	0		
Puerperal fever§	157	19	11	0	7	192	38	7	1	
Scarlet fever	434	33	49	17	7	1,169	43	55	35	15
Tuberculosis:										
Respiratory	324	41	68	7		465	49	83	10	
Non-respiratory	42	3	11	3		39	5	8	2	
Whooping-cough	629	22	51	9	31	916	84	230	3	31

DEATHS	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		3	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	1	1	0	0	3	0	0	1	0
Influenza	28	0	0	0	0	36	2	1	0	0
Measles	0	0	0	0	0	0	0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	571	42	23	12	7	669	39	27	14	7
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever	0	0	0	0	0	0	0	0	0	0
Tuberculosis:										
Respiratory	74	7	5	0	3	79	4	3	4	1
Non-respiratory		0		0	1			0	1	2
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	343	39	25	8	7	367	25	24	4	11
Deaths (excluding stillbirths)	10,703	836	590	121	164	11,158	894	642	163	179
LIVE BIRTHS	16,424	1288	1180	223	287	15,958	1298	1099	319	361
STILLBIRTHS	73	34	29			327	27	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Medical Statistics, London University

Dr. P. ARMITAGE, a member of the Statistical Research Unit of the Medical Research Council at the London School of Hygiene and Tropical Medicine, has been appointed to the London University chair of medical statistics tenable at that school from October 1. He succeeds Professor A. BRADFORD HILL, F.R.S.

Dr. Armitage, who was born in 1924, first went up to Cambridge in 1942, but his university career was interrupted by the war, and he spent 1943 to 1945 in the statistical advisory department of the Ministry of Supply, and 1945 to 1946 in the mathematics division of the National Physical Laboratory, Teddington, before returning to Cambridge in 1946. He took a First in the Mathematical Tripos, Part II, in 1947, the year in which he took up his present appointment. He gained his Ph.D.(Lond.) in 1951. He has been part-time lecturer at the London School of Hygiene and Tropical Medicine since 1948. Dr. Armitage's publications include *Sequential Medical Trials* (1960), and various chapters and articles. He has been honorary secretary of the Royal Statistical Society since 1958.

Prizes for Papers on Anaesthesia

The Association of Anaesthetists of Great Britain and Ireland is offering three prizes for papers based on research in anaesthesia or related subjects. Entrants need not be members of the association. Full details are obtainable from the honorary secretary, Association of Anaesthetists of Great Britain and Ireland, 47 Lincoln's Inn Fields, London W.C.2, to whom entries must be submitted on or before March 30, 1962.

Society for General Microbiology

The Society held its annual general meeting on April 10 at the Royal Institution. For the forthcoming year the officers of the Society are: *president*, Professor R. LOVELL; *treasurer*, Professor K. E. COOPER; *editors*, Professor B. C. J. G. KNIGHT and Mr. A. F. B. STANDFAST; *meetings secretary*, Dr. B. W. LACEY; *general secretary*, Dr. S. T. COWAN. The Marjory Stephenson Memorial Lecture, "The Development of Microbiology," was given by Professor B. C. J. G. KNIGHT and a symposium on the microbial reaction to environment was held on April 11 and 12. The subject of the Society's symposium in 1962 will be microbial classification.

Health in Fiji

The Medical Department of Fiji reports that 1959 was a record year in the campaign against leprosy there: 131 patients with leprosy were discharged as cured from the centre on Makogai Island; there were only three deaths; and the number of patients remaining at the centre at the end of the year was reduced to 317. The money spent on public health in the Territory continued to increase. In 1950, when the population was 293,764, expenditure was £1 7s. 2d. a head a year; by 1959, with a population of 387,646, more than £900,000 (or £2 4s. 2d. a head) was spent on medical and health services. This represented 10% of the Colony's expenditure during the year.

Training for Surgical Shoemaking

The City and Guilds of London Institute is starting a part-time study scheme to provide examination qualifications in surgical shoemaking. The number of shoemakers is declining and few boys are training for this work, which requires a high degree of craftsmanship. Inquiries about the scheme should be sent to the Institute, 76 Portland Place, London W.1.

British Association of Physical Medicine

The annual dinner of the British Association of Physical Medicine was held in the Hall of the Society of Apothecaries on April 21, with the president, Dr. HUGH BURT, in the chair. Mr. H. J. SEDDON, proposing the main toast of the evening, said that in the 18 years of its existence the association had brought about great improvements in the practice of physical medicine, and one of the ways it had done this was to discourage some of the eccentricities of those who were pioneers in this branch of medicine. But the development of physical medicine had been patchy, and four-fifths of those who practised this specialty lived south of a line from the Severn to the Wash. It was the same with neurologists. Mr. Seddon found this disquieting, and urged that steps should be taken to overcome ignorance and misunderstanding about physical medicine. A good deal of the treatment used in physical medicine was still in the empirical stage, and more understanding was needed of the methods specialists in physical medicine so skilfully employed. In reply, Dr. HUGH BURT said that their association helped to bridge the gap between orthopaedic surgery and physical medicine, and referred to the successful meeting the association had just had at the great orthopaedic centre at Stanmore. Dr. R. M. MASON proposed the health of the guests, and Mr. A. C. H. BELL, President of the Royal College of Obstetricians and Gynaecologists, replied.

London–Bombay Radio Discussion

On April 22 a panel of doctors in London discussed by radio the problems of tuberculosis with a similar panel in Bombay. Those taking part in London were Dr. W. D. W. BROOKS, Dr. K. M. CITRON, Dr. N. L. RUSBY, and Mr. T. HOLMES SELLORS. The Indian panel were Dr. B. B. YODH, Dr. M. D. DESHMUKH, Dr. GEORGE COELHO, Mr. B. R. BILLIMORIA, and Dr. V. D. ARORA. The programme was sponsored by Smith Kline and French (India) Ltd.

COMING EVENTS

Institute of Dermatology.—Exhibition, "Dermabrasion," May 3–27, by Dr. BRIAN RUSSELL and Dr. D. C. G. BETT (first of a series of semi-permanent exhibitions available during the Summer Term). Details available from the Secretary of Institute, Lisle Street, London W.C.2.

Bristol University Department of Psychiatry.—Exhibition, "Bristol in the Evolution of Mental Health 1696–1961," May 4–24, Royal West of England Academy of Art, Queens Road, Bristol 8.

Croonian Lectures.—Professor J. MCMICHAEL, F.R.S., "Reorientation in Hypertensive Vascular Disorders," May 9, 11. See advertisement p. 53.

Alfred Adler Medical Society.—Dr. A. K. GRAF, "Helping the Delinquent Child," May 11, 8 p.m., 11 Chandos Street, London W.1.

Territorial Army Medical Officers Association.—Annual dinner, May 13, 7.30 p.m. for 8 p.m., Officers' Mess, Keogh Barracks, Mytchett. Annual general meeting of T.A.M.O.C. in Mess, 7 p.m. Overnight accommodation available. Details and application form from Colonel J. A. DUDGEON, 41 Flood Street, London S.W.3.

Cambridge University Medical School.—Symposium, "The 'Allergic' Diseases of Childhood," May 13, 10.30 a.m. to 4.30 p.m., Addenbrooke's Hospital, Cambridge. Programme: Dr. R. R. A. COOMBS, "A Simple Classification of Allergic Phenomena"; Dr. A. J. ROOK, "Eczema in Infants and Children"; Dr. DOUGLAS GAIRDNER, "Asthma in Childhood"; Dr. R. C. ROXBURGH, "The Infant that Fails to Thrive." Clinical cases will be demonstrated by Dr. JANET ROSCOE and others. Applications by May 6 to the Secretary, Cambridge University Medical School, Tennis Court Road, Cambridge.

British Council for Rehabilitation of Disabled.—Annual general meeting, May 18, 3 p.m., H.Q.S. *Wellington*, Temple Stairs, Victoria Embankment, London W.C.2.

Dijkzigt Hospital, Rotterdam.—Conference, May 27. "Prevention of Thrombo-embolism in Surgery." Details from Dr. J. M. GREEP, Surgical Department, Dijkzigt Hospital, Rotterdam, Holland.

University of Cambridge Postgraduate Medical School.—Symposium, "Tracheostomy and Artificial Respiration," May 27, Addenbrooke's Hospital, Cambridge. Details from Secretary of Medical School, Tennis Court Road, Cambridge.

2nd International Conference, International Psychosomatic Cancer Study Group.—Paris, August 27–29. Theme: "Psychosomatic Aspects of Neoplastic Disease." Details from United Kingdom representative, Dr. D. M. KISSEN, Brookfield, Elm Walk, Bearsden, Glasgow.

International Union of the Medical Press.—The Fifth Congress of the International Union of the Medical Press will be held in Turin from June 9 to 11, 1961, under the joint presidency of Professor M. LOEPER, of Paris, and Professor T. OLIARO, of Turin. It will be one of several international and national medical and surgical conferences being held in Turin between June 3 and 15. In addition to the International Festival of Medical Films (see *Journal*, January 21, p. 220), there will be an International Exhibition of Health and Hygiene sponsored by the medical publishing firm of Minerva Medica and the Italian Medical Association. Turin will also be the main centre of the celebrations this summer commemorating the unification of Italy 100 years ago. Inquiries to the Secretary-General, Minerva Medica, 83–85 Corso Bramante, Turin, Italy.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

ARCHIVES OF DISEASE IN CHILDHOOD

Acute Haematogenous Osteomyelitis with Special Reference to Osteitis of the Neck of the Femur. J. H. Louw and B. Shandling.
Recurrent Urinary Infection in Girls. D. Innes Williams and D. E. Sturdy.
Endemic Urinary Lithiasis in Turkish Children. Herbert B. Eckstein.
Congenital Abnormalities of the Anus and Rectum. Malcolm H. Gough.
From the Mermaid to Anal Imperforation: The Syndrome of Caudal Regression. Bernard Duhamel.
Imperforate Vagina in the Newborn. Wallace M. Dennison and Paul Bacsich.
Gastric Atresia. H. Würtenberger.
Autotransplantation in Lingual Ectopia of the Thyroid Gland. Peter Jones.
Juvenile Fibromatosis. Neville K. Connolly.
The Scottish Paediatric Tumour Registry. Agnes R. Macgregor.
British Association of Paediatric Surgeons: Seventh Annual Meeting.
Urinary Tract Duplication in Childhood. J. H. Johnston.
Paediatrics in Freetown, Sierra Leone. F. Stephen Carter.
The Effect of Tropical and Other Environmental Factors on Stature and Subcutaneous Fat in Kampala Nursery School Children. H. F. Welbourn.
The Influence of Maternal Iron-deficiency Anaemia on the Haemoglobin of the Infant. Philip Lanzkowsky.
Congenital Thrombocytopenic Purpura Treated by Exchange Transfusion. J. M. Bridges and I. J. Carré.
Two Outbreaks of Neonatal Skin Sepsis Caused by *Staphylococcus aureus* Phage Type 71. C. H. L. Howells and H. Everley Jones.
Neonatal and Maternal Serum Transaminase Activity at Birth. I. Kessel and W. M. Politzer.
Foetus in Foetu and the Retroperitoneal Teratoma. R. H. Lewis.
Paediatric Pathology Club. Proceedings of the Sixth Annual Meeting.
Book Reviews.

Volume 36, No. 186. (Bi-monthly; £4 4s. annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

The History of the Moorfields Medical School. C. Cook.
Some of the Great Historical Figures Associated with Moorfields. T. Keith Lyle.
Influence of the Facial Nerve on Intra-ocular Pressure. J. Gloster.
Intracapsular Extraction of Intumescent Cataract by Application of Low Temperature. T. Krwawicz.
Ocular Lesions after Treatment with Chloroquine. H. E. Hobbs, S. P. Eadie, and F. Somerville.
Formed Elements in the Human Lens Capsule. A. J. Dark.
Intravenous Urea in Glaucoma. C. G. Keith.
Method for Keratographic Recording. R. Plummer and A. Lamb.
Sachs's Medium for the Storage of Donor Eyes. D. J. Fitzmaurice.
Correspondence.
Book Reviews.
Notes.
Obituary.

Volume 45, No. 4. (Monthly; £6 annually. With *Ophthalmic Literature* and Index, £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 1

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. P Strickland: Clinical Effects of Ionizing Irradiation on the Skin.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. E. J. Moran Campbell: Neurology of Respiration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. C. A. Clarke: Application of Genetics to Clinical Medicine.
ST. MARY'S HOSPITAL MEDICAL SCHOOL: WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., First Almroth Wright Lecture by Professor J. N. Morris: Studies in Cardiovascular Disease.

Tuesday, May 2

LONDON UNIVERSITY.—At School of Pharmacy, Brunswick Square, W.C., 5.30 p.m., special university lecture in physiology by Professor Hallowell Davis (Missouri): Some Principles of Sensory Action.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Dr. H. E. Lewis and Dr. J. P. Masterton: Polar Physiology—Its Development in Britain.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. Noel Gosse: Changing Face of Obstetrics.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Some Cases of Neuroradiological Interest.

Wednesday, May 3

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Dr. L. G. Norman: Medical Aspects of Road Safety.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Skin Changes Due to Degeneration in the Corium.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Open Lecture by Mr. N. R. Barrett: Bronchial Carcinoma: Send us the Cases Early!
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. L. Jeanes: clinical pathological conference.
LEWISHAM GENERAL HOSPITAL.—5.45 p.m., Mr. I. M. Hill: Assessment of Mitral Valve Disease.
PLYMOUTH MEDICAL SOCIETY.—3 p.m., visit to Ellbridge Experimental Horticultural Station.

Thursday, May 4

LONDON UNIVERSITY.—(1) At School of Pharmacy, Brunswick Square, W.C., 5.30 p.m., special university lecture in physiology by Professor Hallowell Davis (Missouri): From Sound to Nerve Impulses. (2) At Senate House, 5.30 p.m., special university lecture in microbiology by Professor R. Y. Stanier, Ph.D. (California): Bacterial Photosynthesis.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Dr. V. Smallpeice: Growth and Nutrition from the Paediatrician's Viewpoint.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. E. J. Moran Campbell: Diagnosis and Management of Respiratory Failure.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Otolaryngology Lecture by Dr. R. Bodley Scott: Blood Diseases in Relation to Otolaryngology.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: HOME COUNTIES BRANCH.—2 to 4.30 p.m., visit to Road Research Laboratory, Traffic and Safety Division, Crowthorne, Berks.

Friday, May 5

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: clinical demonstration
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. J. C. Hogg: Nasal Obstruction.
MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, London W.C., 5.30 for 6 p.m., discussion to be opened by Dr. A. B. Kinnier Wilson: Artificial Muscles.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. R. S. Lawrie: Carcinoma of the Mouth.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Mr. A. J. Gardham: Carcinoma of the Mouth.

Saturday, May 6

FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—10.30 a.m., scientific meeting. Subject: Hypothermia.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10 a.m., Professor O. Lowenstein: Evolution of Static and Acoustic Sense Organs; Dr. Hallowell Davis (St. Louis): Relation of Presbyacusis to Noise-induced Hearing Loss; Dr. Jürgen Torndorf (Iowa City): Cochlear Hydrodynamics.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Chambers.—On April 14, 1961, at West Middlesex Hospital, to Barbara June (formerly Rowe), wife of Dr. D. R. Chambers, a sister for Mark and Lynn—Judith Elizabeth.
Clark.—On April 10, 1961, at Burton General Hospital, Burton-on-Trent, Staffs, to Drs. Margaret (formerly Johnson) and Roger Clark, a son—Simon David.
Lipman.—On April 6, 1961, at University College Hospital, London W.C., to Nahid (formerly Sahim), wife of Dr. Harald M. Lipman, a daughter—Amanda Zohreh.
Oddy.—On April 19, 1961, at 9 Farmhouse Lane, Pogmoor, Barnsley, Yorks, to Doreen (formerly Jones), S.R.N., S.C.M., wife of Dr. C. G. Oddy, a son—Duncan Robert.

DEATHS

Barrett.—On April 8, 1961, at Northwich, Cheshire, Alan John Barrett, M.R.C.S., L.R.C.P., Surgeon Commander, R.N.
Smith.—On April 3, 1961, at Wyke House, Isleworth, Middlesex, George William Smith, O.B.E., M.B., Ch.B., aged 84.
Sparks.—On April 2, 1961, at Hill Head, near Fareham, Hants, Clifford William Sparks, *M.C.*, M.R.C.S., L.R.C.P., aged 70.
Sykes.—On March 31, 1961, in hospital, William Stanley Sykes, M.B.E., D.A., M.B., B.Chir, D.P.H., of Glenholme, Morley, Leeds.
Thomson.—On April 1, 1961, at Holland House, Harray, Orkney, William Traill Thomson, M.R.C.S., L.R.C.P.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Immunization and Epilepsy

Q.—*Is immunization, including smallpox vaccination, contraindicated in children with epilepsy or an epileptic family history? Are some types of immunization more contraindicated than others?*

A.—Only whooping-cough vaccine is definitely contraindicated. This is because of the risk of an encephalopathy occurring after the injection—a risk which is normally very slight but considerably enhanced in a person with a history of convulsions. Smallpox vaccination might be thought by many to be contraindicated, and should perhaps not be done in children of school age unless there is a definite risk of exposure or necessity (for example, in the case of international travellers). Almost all younger children with a personal or family history of convulsions should probably be vaccinated if their general health is good. There is not likely to be an untoward reaction after any other immunological procedure, and, on general principles, it would be desirable to administer the usual vaccines and, when specially indicated, antisera.

Sterilizing Telephones

Q.—*Is it necessary to sterilize telephone handpieces, and what would be the most effective method?*

A.—The best answer to this question is to be found in the work of R. E. O. Williams,[1] who examined swabs from the mouthpieces and earpieces of 105 telephones in offices and 48 in public kiosks in central London. He did not confirm the findings of earlier workers, who found such organisms as tubercle bacilli and haemolytic streptococci on them. Apart from a single isolation of a pneumococcus, the only pathogenic organism was *Staph. aureus*, which was found on 7% of mouthpieces and 18% of earpieces. Experiments were al o done to determine whether a jet of air at least as powerful as that produced by speaking into a mouthpiece would detach bacteria from it, and it did not. It seems, therefore, that unless the lips actually touch the mouthpiece, which in ordinary telephone conversation they do not, infection from this source is unlikely: the only danger is that of planting someone else's staphylococci on one's ear.

It is certainly not possible to "sterilize" telephones, and doubtful whether any sufficiently innocuous chemical would even disinfect them and keep them free of pathogenic bacteria for any length of time. Regular "disinfection" of mouthpieces of many of the office telephones examined was carried out weekly by a commercial firm. These were cleaner than others, but the bacterial content of 36 swabbed the day before "disinfection" and 31 swabbed on the day after it differed little, either from each other or from that of mouthpieces not so treated.

REFERENCE

[1] *Monthly Bull. Minist. Hlth Lab. Serv.*, 1954, 13, 52.

Allergy to Plastic Dentures

Q.—*A woman suffers from angioneurotic oedema, principally of the face, and at one time had a skin rash due possibly to allergic reaction to plastic beads. May her angioneurotic oedema be due to her plastic denture? Is there a diagnostic test?*

A.—It is very unlikely, though not impossible, that the angioneurotic oedema in this case is due to a plastic denture. The plastic beads presumably caused a contact dermatitis. One would expect involvement of the mouth if the dentures were causing trouble. Diagnostic tests are not entirely reliable. The denture, or a scraping from an exactly similar denture, could be strapped on to the forearm and allowed to remain there for forty-eight hours. If the response was negative, testing against the buccal mucous membrane could then be tried. Details of testing for denture sensitivity are available.[1]

REFERENCE

[1] Urbach, E., and Gottlieb, P. M., *Allergy*, 1946, 2nd edition. Heinemann, London.

Changing from Insulin to Chlorpropamide

Q.—*A woman aged 72 is adequately stabilized on a single daily injection of 40 units of lente insulin. Her vision is now failing, with consequent difficulty in managing the injections, and she is anxious to use an oral hypoglycaemic agent. Should a change be contemplated in these circumstances? If so, how should it be managed, which preparations should be used, and in what dosage?*

A.—It may not be possible to change to oral hypoglycaemic agents, since patients receiving as much as 40 units of insulin are usually regarded as unsuitable. However, in the present case a trial would be justified. Insulin should be withheld for a few days, during which the urine should be tested frequently for sugar *and* ketones. If there is any evidence of ketonuria the trial must be abandoned. If all goes well, chlorpropamide may be substituted in a single morning dose of 300 mg. Control can then be assessed by testing urine passed in the late afternoon and again some hours after the evening meal, and the dose adjusted accordingly.[1]

REFERENCE

[1] *Brit. med. J.*, 1961, 1, 188.

Lead Absorption from Gun-shot Pellets

Q.—*Many people have lead gun-shot pellets lodged in their bodies. Is it possible for lead absorption and poisoning to result?*

A.—The question whether lead poisoning can occur as a result of the absorption of lead from missiles such as bullets, pieces of shrapnel, or gun-shot pellets retained in the body has long been a subject of discussion. The consensus of opinion appears to be that this may occur. Salter[1] says that lead poisoning has been described repeatedly from this source and that it is often seen in birds, which develop a characteristic "wing-drop" analogous to the wrist-drop of lead palsy in man. Leschke[2] states that, under certain circumstances, gun-shot injuries in which the missile remains in the body can give rise, even years later, to symptoms and signs of lead poisoning. He quotes seven cases. Three of these were associated with lead shot, but the clinical description of them leaves some doubt as to whether the diagnosis of lead poisoning was justified. The subject was also reviewed by Machle,[3] who found more than forty cases of lead poisoning attributed to missiles dating back to 1867. Of these cases, the majority were due to bullets, but eleven were associated with shot of various kinds.

Few of these cases would satisfy modern criteria for the diagnosis of lead poisoning. The clinical features in most of them were atypical, and biochemical analysis for the presence of lead in the blood and urine had either not been performed or had been done by somewhat crude methods. Machle himself described two cases, both associated with pistol bullets. In one of these a high lead content in blood and urine was demonstrated, and this fell significantly after removal of the bullet.

In view of the large number of people who are going about with retained missiles of one kind or another, the occurrence of clinical lead poisoning from this source must be very rare. It can sometimes be shown by *x*-ray examination that lead is being absorbed from a retained missile and is being deposited locally in the surrounding tissues. It also seems quite certain that such people may have a raised level of lead in the blood and an increased urinary excretion of lead, but this does not necessarily mean that they are

suffering from lead poisoning. It is now known that the urinary excretion of δ-amino-laevulic acid is a very sensitive indicator of whether a patient has metabolically active lead in his body, and it would be interesting to know whether persons with retained metallic foreign bodies containing lead have an increased excretion of this substance.

REFERENCES
1 Salter, W. T. *A Textbook of Pharmacology*, 1952. Saunders, London and Philadelphia.
2 Leschke, E., *Clinical Toxicology*, 1934. Churchill, London.
3 Machle, W., *J. Amer. med. Ass.*, 1940, **115**, 1536.

Treatment of Chloasma

Q.—*Is there any treatment for removing the brown stains which occur on the face of some women during pregnancy?*

A.—The treatment of chloasma is not very satisfactory. Monobenzone ointment (monobenzyl ether of hydroquinone) may be used and is sometimes successful, but there is a risk of provoking contact dermatitis. The pigmentation can be masked by cosmetics.

Depth of Graves

Q.—*I gather that the usual recommended depth of graves is that no part of the coffin must come within 3 ft. (0.9 m.) of the ground surface, but if soil conditions are suitable 2 ft. (0.6 m.) may be permitted. On what public health or other grounds have these figures been arrived at?*

A.—Regulation 8 of the Regulations made by the Home Secretary for burial grounds provided under the Burial Acts, 1852, 1853, 1854, 1855, and 1857, is as follows:

> No coffin shall be buried in any unwalled grave within 4 ft. (1.2 m.) of the ordinary level of the ground unless it contains the body of a child under 12 years, when it shall not be less than 3 ft. (0.9 m.) below that level.

The depth of the average adult coffin is 15 in. (38.1 cm.) and that of a child under 12 years is not more than 12 in. (30.4 cm.). This allows a 2 ft. 9 in. (0.8 m.) coverage of earth for an adult and at least 2 ft. (0.6 m.) for a child. The purpose of this earth coverage is, of course, to seal off noxious effluvia resulting from decomposition of the body.

The considerations to be borne in mind in this connexion are discussed in a Ministry of Health memorandum on the Sanitary Requirements of Burial Grounds, issued in May, 1926.

Idiopathic Auricular Fibrillation

Q.—*What is the prognosis of idiopathic auricular fibrillation in an otherwise fit man aged 34, in whom fibrillation started abruptly 18 months ago and has persisted ever since? There was an attack of fibrillation for a few days only about 11 years ago. He is normotensive, has no mitral stenosis, and thyrotoxicosis has been excluded. Attempts to correct the arrhythmia by quinidine, etc., were unsuccessful. Daily digitalis keeps the heart rate at about 80 per minute.*

A.—Idiopathic or lone atrial fibrillation can cause congestive heart failure in about 10% of patients,[1] and may reduce effort tolerance. Digitalis is apparently not always adequate to control heart failure in the small percentage of patients who have this complication, even when the ventricular rate is well controlled. Conversion to sinus rhythm by quinidine, however, may result in complete cure.[2] In the majority of patients, when the ventricular rate is satisfactorily controlled with digitalis, symptoms are usually slight and prognosis good. There is no certain tendency to left atrial thrombosis and embolism, and life is not commonly threatened or activity impaired.[3] If the diagnosis is correct in the patient quoted, no undue anxiety need probably be felt, but, since quinidine has been unsuccessful, digitalis should be maintained indefinitely to control ventricular rate.

REFERENCES
1 Phillips, E., and Levine, S. A., *Amer. J. Med.*, 1949, **7**, 478.
2 Wood, P., *Diseases of the Heart and Circulation*, 2nd ed., 1956. Eyre and Spottiswoode, London.
3 Evans, W., *Cardiology*, 2nd ed., 1956. Butterworth, London.

Antidiabetic Drugs in Disseminated Sclerosis

Q.—*Is there any evidence that oral antidiabetic drugs are of value in disseminated sclerosis?*

A.—The cause of multiple (disseminated) sclerosis remains unknown. Among the many possibilities which have been considered, one hypothesis is that the disease is due to a fundamental disorder in carbohydrate metabolism. This view is supported by the finding that some patients with multiple sclerosis have an abnormal response to oral glucose and other abnormalities of carbohydrate metabolism such as an increase in the amount of lactic and α-ketoglutaric acid in the blood.[1 2] These results have been interpreted as indicating that there is some defect in the utilization of small carbohydrate molecules. If this hypothesis were correct, then substances which have an effect on carbohydrate metabolism might influence the course of multiple sclerosis.

A preliminary report on the use of the antidiabetic sulphonamides by Sawyer[3] is encouraging. He treated seven patients with tolbutamide in a dosage of 0.5–1.5 g. daily. In all cases definite improvement was noted while the patient was receiving capsules containing tolbutamide, and deterioration occurred when similar capsules containing sugar were substituted without the patients' knowledge. Sawyer also found that a high carbohydrate diet made these patients worse and that a diabetic diet low in carbohydrate had the reverse effect. It is to be emphasized, however, that this is only a preliminary report and that the number of patients is small. In a condition such as multiple sclerosis, in which remissions and relapses are frequent and in which the criteria for improvement are largely subjective, considerable confirmation of these results will be required before it can be claimed that the sulphonylureas are any better than the many other substances which have had a brief heyday in the treatment of multiple sclerosis and in the end have been found to be ineffective.

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2 Henneman, D. H., Altschule, M. D., Goncz, R. M., and Alexander, L., *A.M.A. Arch. Neurol. Psychiat.*, 1954, **72**, 688.
3 Sawyer, G. T. *J. Amer. med. Ass.*, 1960, **174**, 470.

Swimmer's Cramp

Q.—*What is the cause of swimmer's cramp? Is there anything to prevent it, other than avoiding the cause?*

A.—I do not know the cause of swimmer's cramp. However, there seems little doubt that it is far more frequent in cold water than in warm, and that the longer in cold water the more likely is cramp to occur. So muscle cooling is probably the most important factor. Another feature is dehydration—e.g., from vomiting. Long-distance swimmers frequently vomit, partly because of swallowing sea-water, or possibly even as a form of sea-sickness.

Correction.—In the first paragraph of the section headed "Research and Finance" in the article on "William Harvey's Lessons for To-day" (April 22, p. 1123), the sentence "but his dedication of his book to King Charles II . . ." should have read ". . . to King Charles I." Robert Boyle died in 1657, not 1557 as stated.

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